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ABSTRACT

This progress report is based on seven years of basic research in maternal health, child health and human development. Topics include: The Beginning of Life: Prenatal Development; Early Prevention, Detection, and Therapy of Congenital, Structural and Metabolic Defects; Problems of Birth and Postnatal Adaptation; Child Development: Normal and Abnormal; The Reproductive Process: Basic Biology and Its Relation to Family Planning; Family Planning, Maturation and Aging. Trends in funding and program development are also listed. (WY)

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CHILD AND HUMAN DEVELOPMENT : PROGRESS 1963-1970
National Institute of Child Health and Human Development

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PREFACE

Since the dawn of time, man has been continually seeking ways to improve his lot. He has invented tools and machines to aid him in his quest for knowledge by exploring the remote segments of his own planet and developing technology to carry him onto the surface of the moon.

These accomplishments can be viewed in relation to the discoveries man has made concerning the intricate workings of his own body. Man has found it possible to cure many of the ills that afflict him. He has discovered procedures to repair and adjust the cells, tissues, and organs that sustain his life and make that life more fruitful.

These findings are indeed astonishing, but the amount that remains to be investigated about the human life process staggers the imagination. Man is born, matures, ages, and dies. Why the body changes with age is still a mystery. Why some children are born with a defective brain or a crippled body is yet to be fully understood. How man's own living habits and the conditions surrounding him affect his personality and development are the subject of continued detailed studies. What prompts populations to reproduce at certain rates, and how these ever-increasing numbers of people affect the quality of the life of man, are under intense investigation.

To aid in this search for discovery, the National Institute of Child Health and Human Development was established in 1963 within the National Institutes of Health. Through the Institute's funding mechanisms, research and training are being supported in areas relat-

ing to maternal health, not on any one particular continuing process of growth from reproduction and childhood and on into ma-

Investigators seeking answers to the problems within the purview of the biological, behavioral, and diverse disciplines further

The results of immediately evident in as short a time in the future health laboratory findings must be applied to human population

Within these important findings of scientists who have received support to support research be born free from mental physical and intellectual warding life under those with his fellow man.

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ing to maternal health, child health and human development, focusing
not on any one particular disease or part of the body but on the con-
tinuing process of growth and development, biological and behavioral,
from reproduction and prenatal development through infancy and
childhood and on into maturation and aging.

Investigators throughout the United States and abroad are
seeking answers to the pressing medical and environmental problems
within the purview of the Institute's mission, utilizing the expertise of
biological, behavioral, and social scientists. The collaboration of these
diverse disciplines further exemplifies the unique nature of the NICHD.

The results of productive research are sometimes not imme-
diately evident in as short a time as seven years. Research is an invest-
ment in the future health of mankind. What appears to be promising
laboratory findings must be cautiously interpreted and judiciously ap-
plied to human populations.

Within these pages are set forth some of the more signifi-
cant findings of scientists working within the Institute as well as those
who have received support from the NICHD. It is the goal of the Insti-
tute to support research that, when applied, will enable every man to
be born free from mental and physical disorder; to advance to his full
physical and intellectual potential; and to live a longer and more re-
warding life under those conditions which insure peace and harmony
with his fellow man.

Gerald D. LaVeck, M.D.
Director
National Institute of Child Health
and Human Development

PERSPECTIVE

"Every man is a fluid that becomes solid . . . a history in the making, a personality that is being created. And our progress, or our disintegration, depends on physical, chemical, and physiological factors, on viruses and bacteria, on psychological influences, and, finally, on our own will."

**Man, the Unknown (1935)
Alexis Carrel, Nobel
Prize winner in medicine
and physiology**

By the early 1960's, dramatic inroads had been made against many of the diseases of adults and children through a vast medical effort stimulated by the Federal Government. The National Institutes of Health had been organized to fight specific diseases of man through aggressive programs of research and training. But there was no national resource that concerned itself solely with the biological and behavioral development of the whole person, whether normal and healthy or abnormal or diseased, from conception through old age.

Realizing this vital need, dedicated individuals—physicians, biological and behavioral scientists, civic leaders, legislators, and parents—joined forces to provide such a resource. In 1963, the National Institute of Child Health and Human Development was established—in accord with the goals of NIH—yet with a unique mission broader than that of its sister Institutes.

Within the NICHD purview, man is seen through the combined perspectives of many scientific disciplines. The macromolecules that determine his genetic identity and development from conception are as much a matter of interest as the hormones that regulate his fertility; the long-term effects of his expectant mother's diet are as much a matter of study as his own childhood and adult eating habits; the development and aging of both his mind and his body are of great concern, as are the myriad factors—biochemical, neurological, psychological, social, and ecological—that underlie their functions.

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Probably the most important aspect of the approach of the Institute is the commitment to studying human development from conception through old age. Implicit in this orientation is a strong concern with time, and the way organisms change with its passage. The studies, conferences, and training programs supported by the Institute often demand a high degree of interdisciplinary cooperation, as traditional and time-bound professional demarcations are bridged. For example, a study to trace the relation between maternal health, prematurity, and subsequent individual intellectual and physical development may require the cooperation of the obstetrician, the pediatrician, the endocrinologist, the biochemist, and the psychologist. By pooling data from these multidisciplinary sources, a rich store of information can be developed concerning the mother, the fetus, and his subsequent maturation as a newborn, an infant, and a child. Such a study, extended throughout an individual's life-span, might also enlist the aid of an internist, physiologist, and gerontologist within the medical profession, as well as a host of biomedical and behavioral specialists.

The Institute's concern with changes over time means, too, that it supports a number of longitudinal studies, which show how individuals change as they grow older, as well as more conventional cross-sectional studies, which compare characteristics of different individuals of the same or different ages. The longitudinal study poses special difficulties, both for those who conduct it, and those who support it; it takes many years to accumulate information; requires extraordinary consistency of staffing, subjects, procedures, and support; necessitates the utmost cooperation by all those, young and old, who participate; and demands extreme patience on the part of researcher and sponsor alike.

The problems and questions to which the Institute's personnel and resources are devoted are as difficult as they are important—the biological mechanisms underlying human fertilization, the causes of normal and abnormal development *in utero*, the sources of normal and retarded intellectual and physical growth, the biogenesis of aging. Most of these processes, at the core of man's basic life cycle, will require years of study before sophisticated, comprehensive understanding has been gained. Yet there are already great signs of progress, and in some areas—notably in the care of the pregnant woman, the fetus, and the newborn—lifesaving new techniques have emerged in the few years since the NICHD was established.

This report gleans from the Institute's activities those achievements that typify its approach and represent its impact, both direct and indirect, upon the scientific community and society at large. In the spirit of self-assessment, the report will sum up the progress in research currently under study, and many of the major areas which still elude the scientist's grasp. The advances discussed, chosen to be representative, not exhaustive, will include those that immediately affect the health and well-being of young and old, as well as those more basic biological and behavioral studies upon which improved medical care, and, indeed, a better life for all men ultimately depend.

In discussing the fruits of NICHD research and training efforts, it is recognized that the sources of progress in contemporary science and medicine are many, and represent a complexity of intertwined factors. Even the most solitary of scientists builds his work on the findings and theoretical insights of all those who preceded and taught him, and benefits through his familiarity with the work of his fellow scientists. His support may come from universities, private foundations, and commercial scientific industries, or fellowships, contracts, or grants from numerous governmental agencies. These organizations may simultaneously support various aspects of his work. All, of course, may justifiably claim to have affected the course of his work, and all feel particularly proud when his efforts bear fruit.

How, then, can the Institute's relatively recent contribution to the field of human development be identified? NICHD serves in many roles within the biomedical community: initiator, coordinator, communicator, teacher, evaluator, and catalyst. In some instances, when funding is provided for the research of investigators (whether through the intramural research program or through extramural grants and contracts), the impact of the Institute is direct. At other times, the influence is more subtle: supporting conferences, publishing reports and abstract journals, and underwriting training programs. Frequently, new areas of discussion, research, or training have been opened as a result of the Institute's efforts, and new programs have been established that might otherwise never have been possible.

This report will not attempt to sort these multiple levels of influence and impact on science and the community. At this point in the Institute's development, it is sufficient to show the seeds of understanding it has sown and to harvest some of the first fruits.



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THE INSTITUTE'S GOALS AND ITS SPECIAL APPROACH

The Institute is dedicated to conducting and supporting an integrated program of research into the sequential changes characteristic of individual development from the moment of fertilization through old age and death. This approach, which cuts across disciplines, and spans both normal and abnormal development, provides a sound scientific basis for continuing improvements in the health and well-being of the American people, whatever their ages.

To achieve its mission, the Institute has identified five primary areas for programmatic development, each corresponding to a crucial cluster of problems of both scientific and social importance and urgency: perinatal biology and infant mortality, growth and development, mental retardation, reproduction and population studies, and adult development and aging.

Within the five areas, the Institute recognizes certain goals as preeminent. Its mission may thus be seen as:

- Defining the prerequisites for the optimal development of children

- Understanding the reproductive process and the factors underlying population change

- Realizing the maximum health and well-being for every pregnant woman and her progeny

- Preventing, detecting, and treating mental retardation and improving the intellectual capacity of normal and retarded individuals

- Favorably modifying the biological, psychological, and social changes that occur with aging.

These areas and their attendant goals are intimately related; progress in one area represents an advance in all. By recognizing these interconnections, the Institute is able to address its efforts toward an integrated attack on complex problems that demand an orchestration of approaches. As a case in point, the Institute has been supporting a number of diverse studies that are particularly relevant to the physical, psychological, and social problems of the disadvantaged. By applying

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All over the world, the people who are poorest and live in the most inadequate environments are also those who suffer most from health problems; they and their children die younger than their more affluent countrymen. The absolute degree of poverty is greatest in developing nations, but even in our own advanced and rich country, the poverty cycle is widespread, and its attendant problems are becoming increasingly visible.

A poor American family is often hard-pressed to afford enough food to supply the basic needs of its members, and finds it harder still to supply the full range of foods. For many of the poor, a doctor is seen only when medical care is absolutely urgent; resources for prenatal care, regular checkups, and preventive medicine are not always readily available or are under used, for a variety of reasons. In addition, the psychological and social needs of the aging and aged poor—as well as their physical needs—too often go unmet. Many of the poor are also relatively uneducated; a high birth rate is thus also a frequent part of the poverty cycle. For the woman in poverty, pregnancy often comes early in life, and childbearing is an almost constant state thereafter during her years of fertility. Many of her pregnancies may end in spontaneous abortion, or in premature birth. Her infants, often of low birth weight, stand a greater chance of dying at birth or in early infancy than similar newborns of women of higher socioeconomic levels; they may also stand a greater chance, if they live, of inadequate mental and/or physical development. The children of the poor are likely to have more learning and behavioral problems at school, and may later drop out because of their low motivation and achievement. Because of their lack of education and motivation, such youngsters may be unable to find satisfying work, and so may repeat the whole cycle with a new generation of children.

The Institute has fostered research that may improve the length and quality of life of all Americans, but particularly of those who suffer most from physical and social deprivations. For example, the Institute's reproduction and population research programs, exploring the biological bases of reproduction and contraception as well as the attitudes of various peoples to family planning, promise to bring



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about a wider acceptance of techniques are developments will enable women to space them better, develop healthily, and the productive years when retarded children are in the best of circumstances are more likely because of the

Out of the improved methods of treatment are likely to emerge; the mother and infant in treating developmental problems, particularly the problems of gains for mothers and

The growth research concerning aging deeper understanding of the developing child's development despite social

The men search for the many contributing toward earlier in the development effects of "cultural" learning capacity of Through Institute and retardation Research attacks the problem in retardation has received

The Institute precise diagnosis of middle-aged and aged understanding of the potential social capacities to them; and to longer



about a wider acceptance of family planning, as inexpensive and safe techniques are developed that are simple and effective. Such developments will enable women to have children only when they want them, to space them better so that each child has an optimal chance to develop healthily, and to avoid childbearing in the early and late reproductive years when the risks of bearing premature and mentally retarded children are greatest. In addition, women under such circumstances are more likely to be healthy and well during and after pregnancy because of their reduced childbearing.

Out of the Institute's perinatal biology research program, improved methods of managing pregnancy and maintaining it to term are likely to emerge; these will reduce the health hazards of pregnancy for mother and infant alike. New ways of preventing, diagnosing, and treating developmental problems (both prenatally and at birth), particularly the problems of the newborn infant, are likely to result in special gains for mothers and children living in poverty.

The growth and development program provides support for research concerning nutrition in child development; it is also encouraging deeper understanding of the social and psychological needs of the developing child, and of the means of providing for optimal development despite social deprivation.

The mental retardation program, while continuing the search for the many causes of intellectual deficiencies, is also contributing toward earlier and more precise detection of them. It is supporting the development of new programs that will overcome the retarding effects of "cultural deprivation," and will increase the motivation and learning capacity of children with a variety of learning handicaps. Through Institute aid in establishing 12 multidisciplinary Mental Retardation Research Centers throughout the country, each of which attacks the problem in its own unique way, the effort to overcome mental retardation has received significant new impetus.

The Institute's aging program promises to lead to more precise diagnosis of physical, mental, and social problems of the middle-aged and aged person, whether rich or poor; to greater understanding of the potential of older persons to learn and to expand their social capacities to meet the changing demands of the world around them; and to longer, more fulfilling lives for all.

IMPACT OF NICHD PROGRAMS ON PROBLEMS OF HUMAN DEVELOPMENT

The Beginnings of Life: Prenatal Development

The Genetic Problem: From Genotype to Phenotype

At the beginning of each person's life (except in certain multiple pregnancies) there is one cell: the fertilized egg. From the moment the sperm enters the egg and its nucleus joins with the female cell nucleus, a remarkable sequence of events begins which results, about 266 days later, in the birth of a baby. During this process, one cell becomes 60 trillion or more. Many of the individual's cells will continue to divide throughout the rest of his life, a task of renewal that may well continue for over 80 years. Understanding the process of growth and development by which this exquisite transformation takes place in the uterus, and its relation to the later regeneration and repair of tissues and organs, is a major goal of NICHD.

The search for understanding begins with the process of differentiation by which a single cell becomes the extraordinarily complex organism, made up of billions of specialized cells, that we recognize first as an embryo, then as a fetus, an infant, a child, and, finally, as an adult. This process, as a fundamental aspect of development, is the subject of intensive study by geneticists, cell biologists, biochemists, biophysicists, embryologists, endocrinologists, and others. It represents a common point of interest for all these disciplines and for the multifaceted programs of NICHD.

One of the moments of development deep within the female and attempts to measure. Scientists have therefore attempted to measure development outside the uterus. Differentiation could be studied. Sponsored research has reported that one-cell stages into the two-cell stages subsequently to implantation. These studies had prevented complete stages of a mammalian study of this crucial

Typical of the Institute is one by who is trying to distinguish cells of the developing others are transformed cells, he has found. When chondrocytes significant quantities recognizable as cartilage they can do neither.

The regular first cellular division growth, ultimately of apparatus which originates fertilized egg: 23 pairs of chromosomes, and one pair and one Y sex chromosomes (XX). a complete replication receives, strung along how the cells will divide of the nucleic acid

ON DEVELOPMENT

Development

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One of the problems facing scientists studying the earliest moments of development is that, in mammals, the process takes place deep within the female's reproductive system; observation is difficult, and attempts to measure and control the process are complicated. Scientists have therefore long sought to develop an experimental environment outside the uterus in which the dynamics of fertilization and cell differentiation could be studied. Through the work of two Institute-sponsored researchers, that goal may be more attainable. They have reported that one-cell stages of certain hybrid mice undergo division into the two-cell stages in a simple medium *in vitro*. These two-cell stages subsequently developed into blastocysts capable of uterine implantation. These scientists were thus able to overcome a barrier that had prevented complete development *in vitro* of the preimplantation stages of a mammal. Their discovery opens many new doors to the study of this crucial developmental stage.

Typical of the embryological studies being supported by the Institute is one by an investigator at the University of Pennsylvania who is trying to discover the selective mechanisms whereby certain cells of the developing chick embryo differentiate into cartilage, while others are transformed into muscle. In his study of cartilage-forming cells, he has found that the geometry of tissue may affect function. When chondrocytes are grown in culture as pellets, they synthesize significant quantities of chondroitin sulfate and can form cells that are recognizable as cartilage; but when chondrocytes are grown in layers, they can do neither.

The regulation of processes of fetal development, from the first cellular division to the most elaborate hormonal regulation of growth, ultimately comes under the control of the cellular genetic apparatus which originates in the genetic coding and content of the fertilized egg: 23 pairs of chromosomes consisting of 22 pairs of autosomes, and one pair of sex chromosomes. (Normal males have one X and one Y sex chromosome (XY), while normal females have two X chromosomes (XX).) Each time a cell divides, each daughter cell gets a complete replica of each of the 46 chromosomes, and thus also receives, strung along the chromosomes, the genes that will determine how the cells will develop and grow. Within the genes, the molecules of the nucleic acid DNA contain the "instructions" for this process.



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The Institute supports studies aimed at understanding the process of physical development from the macromolecular level of DNA regulation, through the level of chromosomal organization, to morphological and physiological expression of these basic genetic mechanisms. Considerable attention is given to cell division and replacement throughout the life-span—and to the inability of some cells (muscle, neurons) to provide replacements in adults. Of particular interest, as well, are those disturbances of the normal genetic programming that jeopardize embryonic life, or produce individuals with metabolic, structural, and intellectual defects.

Since 1959, it has been known that abnormalities of the chromosomes can be lethal or lead to physical disability or to conditions such as mental retardation. Down's syndrome, or mongolism, in which the individual has 47 instead of 46 chromosomes, was the first of many chromosomal abnormalities discovered in recent years to be related to characteristic clinical syndromes. The abnormalities may affect the autosomes and/or the pair of sex chromosomes. There may be too many or too few chromosomes, or their shapes may be distorted.

Two Institute grantees at Mount Sinai School of Medicine have recently reviewed the known autosomal abnormalities in man. They conclude that certain chromosomal aberrations may be normal variants, and that even apparently normal individuals may show chromosomal defects.

The Interdependence of Mother and Fetus

From the moment of fertilization to the time the individual enters the world as a newborn, the mother's body systems and placenta serve as the total environment for the developing fetus. No artificial environment has yet been developed which can begin to rival the human original in providing for the physical, chemical, and nutritional needs of the fetus. Yet the adequacy of this natural environment is by no means automatically assured. The general health of the mother, her nutrition, her life-style, and the specific physical, chemical, viral, and other environmental stimuli all contribute to the well-being of the infant growing within her.

The mother not only affects her child's fetal development—she is affected in return. While pregnancy is a normal physiological process, it is also a period of physical and emotional stress for a woman. Special demands are made upon her body to meet the physiological needs of the organism within her, and she undergoes a host of complex biochemical and physical changes that prepare her not only to support, but to deliver the child into the world. Thus, for a woman whose health is already impaired, pregnancy poses special risks for her and her offspring. For other women, latent conditions that might not otherwise have been noticed become more acute. For all women, it is a time requiring wise medical management to assure a normal and healthy course.

The Institute is supporting studies that will lead to increased understanding of both normal and abnormal processes involved in pregnancy and in fetal development, including various aspects of the physiology of pregnancy; disorders of pregnancy; placental function; immunological phenomena; developmental physiology and biochemical processes of fetal growth; the genetic, pharmacological, toxic, and infectious factors that can affect the mother and fetus; and the process of labor and delivery. Institute support is aimed at promoting the maximum health and well-being of every pregnant woman and her progeny. Research results since the Institute's inception have already helped to make this goal more attainable.

It is estimated that about 20 percent of all pregnancies abort spontaneously before the fetus is sufficiently mature to survive in the extrauterine environment. Although these spontaneous abortions may result from abnormalities of the fetus itself, they are also related to the physical condition of the mother. Women with such diseases as chronic high blood pressure, diabetes, and syphilis are particularly prone to abort. Consequently, Institute support is particularly directed toward identifying the pathophysiologic factors that determine which pregnancies have particularly high risks for mother and/or infant, encouraging the development of new ways to reduce those hazards, and finding a rational basis for counseling couples when procreation is likely to pose special medical risks.

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Despite advances in the management of cardiac disease, women with severe heart ailments have generally been advised to forego motherhood rather than undergo the stresses of pregnancy and labor. However, Institute-supported scientists at the State University of New York at Albany have now found, in a retrospective study of the lives of 134 women who became pregnant between 1931 and 1943, that women with rheumatic cardiac disease can bear children without jeopardizing their health or life expectancy. As a result of this study, such women are likely to receive more welcome advice in the future concerning their childbearing potential.

Evidence currently being accumulated suggests that, in addition to other important factors, the state of a woman's nutrition before, during, and after pregnancy (while nursing) may influence both the physical and mental development of her children. Institute-sponsored studies are beginning to clarify the specific nutritional requirements of pregnancy and the biochemical conditions that underlie them. For example, since 1920 it has been known that underfeeding dogs and rats while they were dependent on mother's milk prevented them from ever attaining normal adult size, even when later fed normally. Research supported by the Institute has now shown that a qualitative and quantitative protein deficiency in the diet of mother rats during pregnancy and lactation is associated with incomplete food utilization by their progeny. It has been suggested that in humans, maternal malnutrition during pregnancy may permanently impair the efficiency of children's protein synthesis.

NICHD-supported researchers at the New York Medical College have found, through a new diagnostic test, that a lack of folic acid in pregnancy is a more common nutritional deficiency than was once thought. Both mother and fetus need this nutrient. Nonpregnant women require 50 to 150 micrograms of folic acid in their diets daily, but during pregnancy, this need rises to between 200 and 800 micrograms. A severe lack of this vitamin can lead to megaloblastic anemia of pregnancy, and may possibly cause abortion or developmental defects in the fetus. Megaloblastic anemia can readily be detected by reduction of the normal amount of red blood cells and platelet production in the bone marrow. Now lesser forms of the deficiency that are undetectable

clinically can also be detected by the investigators. In a study of women, as well as of laboratory animals, researchers found that deficiency in the vitamin B₁₂ during pregnancy, or possibly subclinical folic acid deficiency, could lead to the more extreme forms of anemia.

The placenta, which provides the unborn child with nutritive material from the mother's blood, produces products. This versatile organ performs a variety of functions of the endocrine glands, becomes, by itself, a source of hormones necessary for pregnancy, and that may precipitate immunological reactions. It also produces noglobulins, the natural antibodies. Although the placenta can be harmed by harmful substances, other agents may react with it.

The Institute is studying the normal placental function. At New York University, researchers are studying how the placenta is formed. A technique of placental perfusion shows that hormones are transported by which the toxic effects of drugs can be studied.

To gain a better understanding of maternal nutrition to placental development, a scientist, in cooperation with the Pan American Health Organization, compared the cellular composition of the middle-class United States women with the cellular composition of the Indonesian women. The chemical composition of the placenta is also being studied.

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clinically can also be identified through a rapid urine test developed by the investigators. By studying normal pregnant and nonpregnant women, as well as women with complications of pregnancy, these re- searchers found that about 22 percent of the pregnant women were de- ficient in the vitamin, particularly those with twin pregnancies, toxemia of pregnancy, or placental separation. Investigation has shown that subclinical folic acid deficiency is three to four times as frequent as the more extreme form.

The placenta is the organ of transfer between the mother and her unborn child. It produces hormones, transfers oxygen and nu- tritive material from mother to fetus, and carries away fetal waste products. This versatile organ, which alone can perform the diverse functions of the adult lungs, kidneys, intestines, liver, and some glands, becomes, by the fourth month, a main source of hormones nec- essary for pregnancy. It later affects the changes in hormone balance that may precipitate labor and birth. The placenta plays an important immunological role for mother and fetus as well, synthesizing immu- noglobulins, the natural blood ingredients that can prevent infection. Although the placenta can screen the fetus from many potentially harmful substances in the mother's circulation, certain infections and other agents may reach the fetus, placing it at risk.

The Institute has encouraged studies of both normal and ab- normal placental function. In one typical NICHD study, an investigator at New York University has developed a new technique for examining how the placenta in animals responds to various chemicals. Using the technique of placental perfusion, he has examined how estrogen hor- mones are transported, and has identified the protective mechanism by which the toxic effects of steroids on fetuses may be prevented.

To gain greater understanding of the relationship of mater- nal nutrition to placental function and fetal development, an Institute scientist, in cooperation with investigators at the University of Iowa and the Pan American Health Organization in Guatemala, has com- pared the cellular composition of placentas from well-nourished mid- dle-class United States women with those of malnourished rural Gua- temalan women. The investigators have found significant differences in the chemical constituents of the placentas from the two groups. Based





on measurements of DNA and cellular protein, the placentas of the Guatemalan women appeared to contain fewer, but larger cells than those of the United States women. The placental cells of the Guatemalan mothers contained more fat, protein, hydroxyproline, potassium, zinc, and copper, but had less selenium than those of the United States women. These malnutrition-related changes in placental tissue may provide a clue to the ways in which nutritional deficiencies in pregnant women can affect the intrauterine development of their children.

An investigator at the University of Florida has been studying how the placenta affects the acid-base balance in fetuses. He found that the placenta appears to limit the hydrogen and bicarbonate ions that can pass through it. This regulates the acid-base balance in the fetus independent of any potential maternal metabolic disturbances.

Because a healthy placenta is essential to fetal survival, considerable attention has been given to developing simple diagnostic tools to assess how well it is functioning. Studies by several Institute grantees have confirmed that the level of creatinine in a pregnant woman's urine provides a reliable indicator of placental function. By using a simple urine test, physicians can assess the welfare of the fetus, and can decide when to intervene in pregnancy if the survival of the fetus seems to be in question.

Investigators within the Institute are studying the pregnancy-associated enzymes in the blood of expectant women, in the placenta, and in the developing embryo, fetus, and newborn. They have found a way to distinguish between normal and grossly abnormal pregnancies on the basis of enzymatic differences seen in the blood, thus providing a simple diagnostic tool for the early identification of such problems in pregnancy. The investigators hope that by understanding more about the enzymatic role of the placenta and other tissues, they will be able to use maternal blood tests to evaluate fetal health and the course of intrauterine development.

Infectious diseases during pregnancy can jeopardize the development and even the survival of the fetus and harm the mother as well. After the German measles (rubella) epidemic of 1964, many in-

fants of infected mothers had heart disease, blindness, and other defects. Studies of the natural history of these defects and the effects of such diseases on the fetus and how such defects develop are ongoing.

Evidence now suggests that due to specific environmental factors, such as infectious hepatitis, and irradiation, that among 7,000 newborns of sex chromosomes tested in the spring and summer of 1964, there was a high incidence of mongolism during the same period. Studies of sex chromosome aberrations by investigators in other cities have found that X chromosomes (the sex chromosomes involved in mongolism) are often involved in a factor such as a latent viral infection.

Physicians are studying everything a woman ingests during pregnancy may have the potential to become evident. It is an all too recent and too common occurrence that drugs they prescribe, poisons, and the consequences of other substances requiring a prescription, such as LSD, from Institute grantees and abnormal fetal development. New York have analyzed LSD at various times during pregnancy. Other adult "users" were in a control group of nonusers. No apparent congenital defects were found among the LSD users, and no apparent congenital defects were studied.

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fants of infected mothers were born with multiple defects, including heart disease, blindness, and mental retardation. Data from recent studies of the natural history of viral diseases in the pregnant mother and the effects of such diseases on the developing fetus should clarify how such defects develop, and how they can be prevented.

Evidence now suggests that chromosomal defects may be due to specific environmental factors such as German measles, infectious hepatitis, and irradiation. In Denver, NICHD grantees have found that among, 7,000 newborns examined, babies with abnormal numbers of sex chromosomes tended to appear during a five-month period in the spring and summer. There was also an elevated incidence of mongolism during the same period. In addition, they found another cluster of sex chromosome aberrations in a different five-month period. Other investigators in other cities have reported similar clusterings. Possibly X chromosomes (the sex chromosomes) and autosome no. 21 (which is involved in mongolism) may both be susceptible to some external factor such as a latent viral infection in the mother at the time of conception.

Physicians are becoming increasingly aware that almost everything a woman ingests during, and sometimes even before, pregnancy may have the potential for influencing the fetus in ways that may not become evident until birth or even later. The thalidomide story is an all too recent and tragic example. In addition to the effects of the drugs they prescribe, physicians must also be alert to the consequences of other substances such as alcohol, tobacco, drugs not requiring a prescription, and most recently, mind- and mood-altering substances such as LSD. This last has received particular attention from Institute grantees as a possible source of chromosomal damage and abnormal fetal development. NICHD-supported investigators in New York have analyzed the chromosomes of 12 infants exposed to LSD at various times during their fetal life. Their mothers and seven other adult "users" were also studied, and compared with a matched control group of nonusers. While more chromosomal damage was found among the LSD users and their children than among nonusers, no apparent congenital malformations were found among the children studied.

Early Prevention, Detection, and Therapy of Congenital Structural and Metabolic Defects

One of the most exciting medical developments in recent decades has been the recognition that many diseases and abnormalities seen at birth or later in life have their origins in events during embryonic development, and can be prevented or treated if intervention is started soon enough. At the same time, a number of newly discovered techniques have been developed that now make it possible to detect diseases and deformities **in utero**, and, in rare situations, to take appropriate measures to correct them even before the fetus leaves the uterus. NICHD staff activities and support programs have been instrumental in bringing about these developments.

With the relatively new technique of amniocentesis—increasingly used by physicians to gain diagnostic access to fetal tissues and fluids—a needle is injected through the abdomen of a pregnant woman into the amniotic sac surrounding the fetus. A sample of the amniotic fluid within the sac is then drawn off for analysis to detect possible abnormalities, including chromosomal and metabolic defects, as well as to assess the effects of Rh incompatibility. The technique can also be used to identify the sex of the fetus.

By conducting chromosomal and biochemical studies on cells obtained through amniocentesis (which are analyzed directly or

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ing medical developments in recent years that many diseases and abnormalities have their origins in events during embryonic development that can be prevented or treated if intervention is made in time, a number of newly discovered metabolic defects that now make it possible to detect them early, and, in rare situations, to take appropriate action even before the fetus leaves the uterus. Support programs have been instrumental in these developments.

One new technique of amniocentesis—involving percutaneous diagnostic access to fetal tissues through the abdomen of a pregnant woman—allows sampling of fluid surrounding the fetus. A sample of the fluid can then be drawn off for analysis to detect chromosomal and metabolic defects, such as the presence of Rh incompatibility. The technique also allows sampling of the fetus.

Chromosomal and biochemical studies on amniotic fluid (which are analyzed directly or

after being cultured), NICHD-supported scientists at Northwestern University Medical School have now been able to predict whether or not 16-week fetuses will be born with any of a variety of inheritable deficiencies. Their method holds much promise for reducing the number of births of children doomed to mental deficiency.

The amniocentesis technique is also used by Institute-supported scientists to detect the inborn metabolic error that is clinically expressed as the Lesch-Nyhan syndrome. Since this disorder (which involves severe developmental and neurological disturbances as well as overproduction of uric acid) occurs in males having a recessive X-linked mutant gene, it is possible, by determining the sex of the fetus, to tell whether it carries a risk of such a serious chromosomal abnormality. Such information aids parents and physicians in deciding what course of action to take. In some cases, it is now possible to treat the developing fetus, while in others, abortion may be elected.

When infants are born with galactosemia (an inborn absence of the enzyme galactose-1-phosphate uridyl transferase), they are unable to metabolize the galactose normally found in milk products as part of lactose. If their problem goes undetected, they may suffer from growth failure, cirrhosis of the liver, cataracts, and mental retardation, but if treated promptly with a galactose-free diet, they usually develop normally. Investigators at the City of Hope Medical Center in California have now carried out field tests to evaluate two new low-cost, simple methods for detecting this metabolic error in newborns. These tests can easily be combined with current screening programs for phenylketonuria, another inborn metabolic disease, to provide widespread early diagnosis of both diseases.

Advances in the early diagnosis and treatment of fetal and newborn disorders have been particularly dramatic in the management of erythroblastosis fetalis, or Rh hemolytic disease. This blood group condition, which once caused the death of as many as 2,600 infants a year, is now on its way to being eliminated, thanks to the combined efforts of scientists throughout the world, many of whom have received Institute support.

Almost 85 percent of humans have an inherited substance in their red blood cells called the Rh factor. Both those with the factor

("Rh-positive") and those without it ("Rh-negative") are equally healthy. But offspring of an Rh-negative mother and an Rh-positive father may be in danger of developing the potentially fatal jaundice, anemia, spleen enlargement, and even brain damage characteristic of Rh incompatibility. When an Rh-negative mother is exposed to Rh-positive fetal red blood cells (as when the placenta is delivered during birth), she may develop antibodies against the cells that enter in her circulation. In subsequent Rh-positive pregnancies, her antibodies may pass to the fetus and damage its red blood cells, causing the syndrome just described. These same antibodies could also be a hazard to the mother if she received an emergency transfusion without cross matching.

The usual treatment for Rh-hemolytic disease has been to give the newborn infants exchange transfusions, replacing their Rh-positive blood with Rh-negative until the incompatibility has been overcome. However, this technique can only be used with infants who survive until term.

Recently, with the technique of amniocentesis, it has been possible to discover **in utero** whether a fetus has Rh hemolytic disease, to assess the severity of its illness, and even to give intrauterine transfusions to save the infant. An Institute grantee in New York has summarized the success of amniocentesis in Rh-affected pregnancies, and has shown that in about 400 of the pregnancies in which amniocentesis was used, the number of stillbirths and neonatal deaths was nine percent of the total number of Rh-affected babies. When amniocentesis was not used, 30 percent of the Rh-affected babies were either stillborn, or died soon after birth.

Of still greater interest are recent developments in the prevention of Rh sensitization. Several Institute grantees, as well as scientists in England and Germany, have found that if anti-Rh gamma globulin is given to the mother within a few hours of delivery of the first baby, the dangerous antibodies will not be formed. A team of investigators has developed RhoGAM, a highly concentrated solution containing immunoglobulins with Rh antibodies. The immunoglobulins, obtained from the blood of Rh-negative women who have already been sensitized to the Rh factor, apparently suppress the normal im-

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mune response. This preparation, which promises virtually to eliminate Rh incompatibility as a cause of infant morbidity and mortality, has been tested on several thousand women, and is now available to physicians.

Another technological breakthrough in fetal diagnosis has come about through the work of an Institute grantee who has shown that the electrical characteristics of the fetal heart and brain can be monitored to evaluate the well-being of the fetus during labor. For over 50 years, when the heart rate of a fetus deviated from the normal clinical range of 120 to 160 beats a minute, physicians have assumed that the fetus was undergoing fetal distress, and was in grave danger. Even so, the criteria for fetal distress have not been clearly defined, so that paradoxical clinical conditions frequently exist. When seen during labor, this condition is usually acute; it is associated with the recurrent stresses applied to the fetus by uterine contractions, or results from compression of the umbilical cord. Monitoring of the fetal heart rate with a stethoscope, and its interpretation, are particularly difficult during uterine contractions. Therefore, when in doubt, physicians have tended to assume that the fetus was in sufficient danger to warrant performance of a cesarean section rather than proceed with normal labor. Through the use of a new electronic monitoring device developed by this Institute grantee, physicians can now "hear" and compare fetal heartbeats as they occur before, during, and after contractions, and can assess more precisely the state of the fetus and institute the appropriate therapy. One study of the effects of this technique has shown that a dramatic 75-percent drop in the use of primary cesarean sections for fetal distress has occurred in one obstetric service that routinely uses the monitoring procedure.

The physiological meaning of fetal distress (particularly the effects of oxygen deprivation) and the conditions that cause it are being studied by an investigator within the Institute. By monitoring both the brain and heart activity of fetal sheep when oxygen levels were reduced, he found that when a fetus has insufficient oxygen, the first pathological change occurs in the brain's electrical activity and is accompanied by a changed heart rate (too fast, too slow, or uneven). Extensions of this study may lead to new ways of diagnosing and pre-

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In addition to new diagnostic and treatment techniques for the fetus, there has been progress in devising methods to assess and treat the newborn who may be suffering from congenital metabolic defects. Interest has been particularly strong in identifying and modifying conditions that might lead to mental retardation.

An investigator at the University of Wisconsin Medical School has postulated that if newborn macaque monkeys are fed a whole-milk formula containing excessive amounts of certain amino acids, conditions similar to genetically determined inborn errors of metabolism can be induced and duplicated biochemically. These diseases include phenylketonuria, histidinuria, hypoglycemia, and maple syrup urine disease. This potential permits scientists to have a model system for studying these diseases, and suggests that, like phenylketonuria, they may one day be combated, through dietary regulation.

At the Albert Einstein College of Medicine in New York, Institute grantees have been studying the effects of a variety of diets upon the levels of amino acids (such as phenylalanine and tyrosine) in blood serum of low-birth-weight or premature infants. By studying the brain waves of these infants, they have followed the changes and rates of electroencephalographic maturation of the infants' brains as a measure of their developing intellect. These data will eventually be correlated with the nutritional, neurological, and developmental histories of these infants, and will form the basis for comparison with children who are recognized to have some form of mental retardation.

Scientists have recently become interested in studying the diagnostic potential of finger, palm, and sole prints (dermatoglyphics), since certain patterns have been found that are characteristic of a number of clinical disorders, including chromosome defects such as mongolism. Investigators at the University of Minnesota are conducting dermatoglyphic studies of three types of mental retardation not obviously associated with chromosomal errors: phenylketonuria (genetically induced retardation), rubella (environmentally induced retardation), and idiopathic retardation (induced by genetic or environmental factors, or both). The dermatoglyphic patterns of individuals with



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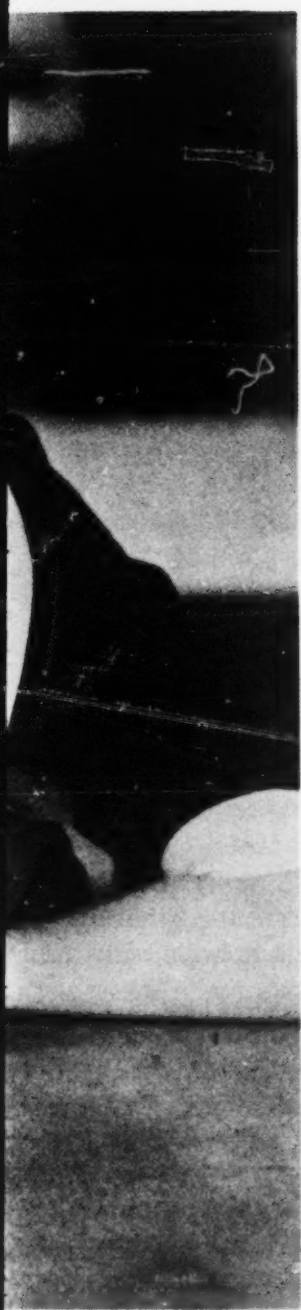
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phenylketonuria and those with idiopathic retardation resemble those of normal controls, but the dermatoglyphic patterns of the rubella group members are abnormal. Apparently an environmental agent like rubella virus can sufficiently alter a fetus early in gestation to change its palm and sole prints. This technique may prove to be a useful tool for identifying intrauterine damage even when chromosomal errors are not present.

At the Institute's Children's Diagnostic and Study Clinic, a combination of sophisticated diagnostic techniques is used to assess and study a variety of intellectually handicapping conditions such as mental retardation, learning disabilities, and sensory-motor defects. Dermatoglyphic, chromosomal, and neurophysiological techniques are all used as diagnostic aids with the handicapped youngsters examined by the Institute staff. In addition, the Clinic staff has discovered chromosomal abnormalities that had not previously been seen.

The detection of infectious diseases in newborns has been aided by the efforts of Institute-supported scientists. A researcher at the University of Alabama Medical Center has studied the significance of gamma globulin levels in umbilical cord serum or plasma specimens of newborn infants. He has found that high serum immunoglobulin levels (particularly gamma M, but also gamma A) result from infections acquired *in utero*, at birth, or postnatally. Immunoglobulin measurement can provide a tool for early diagnosis of newborn infants with clinically inapparent and unusual types of congenitally acquired infections.

Progress in the early diagnosis of congenital deafness in infants has been made through the work of an Institute grantee at Children's Hospital in Washington, D.C. The investigator has developed a new technique for diagnosing auditory defects, using computer-analyzed EEG responses to clicks, tones, and light flashes. The technique has revealed deafness in 12 of 22 infants between one and eight months of age whose mothers had rubella during pregnancy. The EEG test results correlated well with additional clinical and behavioral evaluations. By using this method of diagnosing deafness in infancy, physicians may be able to begin earlier rehabilitation of the deaf child so that his speech and language development may occur more normally.



Problems of Birth and Postnatal Adaptation

It is clear from the statistics on infant mortality that the process of being born and adjusting to the extrauterine world is filled with extraordinary hazards. Of all the children who die before reaching their first birthday, almost three-fourths (the majority of whom are premature or low-birth-weight infants) do not survive their first month—a total of over 50,000 babies yearly in the United States. Most of these deaths (almost 95 percent) result from postnatal asphyxia and incomplete expansion of the lungs; congenital malformation; and other diseases peculiar to early infancy such as developmental immaturity, blood diseases of the newborn, and neonatal disorders arising from certain diseases of the mother during pregnancy:

Initiation of Labor

From conception, a fetus normally requires about 266 days to reach its optimal body weight and a level of physiological maturity sufficient for a satisfactory adjustment to extrauterine life. Yet the birth process sometimes begins prematurely when the fetus has not reached that stage, and the newborn is thrust into a world for which he is not ready. In view of the dominant role of prematurity as a major cause of neonatal deaths, the Institute is concentrating research support toward discovering those factors that are essential to maintaining pregnancy to term, and the factors that initiate the uterine contractions characteristic of labor.

Although specific information is lacking concerning the mechanisms for initiation of labor, whether normal or premature, the

roles of several factors—the fetus itself and its state of development—are still uncertain. Human fetal brains have been observed in farm animals as well as in man to be associated with premature or incomplete development. Additional evidence from studies at the University of Wisconsin indicates that the fetal pituitary gland may be involved in labor. Additional evidence from studies at the University of Wisconsin indicates that the fetal pituitary gland may be involved in labor. Additional evidence from studies at the University of Wisconsin indicates that the fetal pituitary gland may be involved in labor.

Another factor in the process is the hormonal changes during the period of pregnancy and the role of the hormones in the regulation of the hormonal changes. The Institute so that further research can be conducted.

Low Birth Weight and

Although premature birth and low birth weight constitute over 10 percent of the deaths of infants born prematurely annually. The greater the weight at birth, the greater the chance of survival. The greater the weight at birth, the greater the chance of survival.

Many of the factors that influence the development of the fetus are still unknown. The development of the fetus is influenced by many factors, including the mother's health, the mother's diet, the mother's stress, and the mother's environment. The development of the fetus is influenced by many factors, including the mother's health, the mother's diet, the mother's stress, and the mother's environment.

Postnatal Adaptation

Statistics on infant mortality that the adjusting to the extrauterine world is filled with all the children who die before reaching one-fourths (the majority of whom are preterm infants) do not survive their first month—almost entirely in the United States. Most of these result from postnatal asphyxia and infections; congenital malformation; and other deficiency such as developmental immaturity, prematurity, and neonatal disorders arising from complications during pregnancy:

A fetus normally requires about 266 days of growth and a level of physiological maturity for adjustment to extrauterine life. Yet the infant is born prematurely when the fetus has not reached this stage. The dominant role of prematurity as a major cause of neonatal mortality is being studied at the Institute. The Institute is concentrating research support on factors that are essential to maintaining the fetus in the uterus and factors that initiate the uterine contrac-

Information is lacking concerning the process of labor, whether normal or premature, the

roles of several factors are becoming better understood. For one, the fetus itself and its state of development appears to be an important determinant. Human fetuses with either partially or entirely absent brains have been occasionally associated with prolonged gestation. In farm animals as well, cranial and nervous system defects and defective or incomplete development of the pituitary gland have been found to be associated with long gestation periods. These findings suggest that the fetal pituitary gland plays an important part of the initiation of labor. Additional evidence has been provided in studies by investigators at the University of California, who found that when the pituitaries of otherwise normal fetal sheep were partially destroyed, pregnant ewes either failed entirely to commence labor, or did not do so until long overdue.

Another factor apparently associated with initiating the birth process is the hormone relaxin, which primarily affects the latter period of pregnancy and particularly the initial stages of childbirth. Preparation of the hormone from pregnant pigs has been supported by the Institute so that further studies of relaxin's action can be encouraged.

Low Birth Weight and Prematurity

Although prematurely born infants or those with low birth weight constitute over eight percent of all births, they account for 70 percent of the deaths in the neonatal period. Thus, of about 300,000 infants born prematurely or at low birth weight, more than 50,000 die annually. The greater their gestational immaturity or the smaller their size, the greater the hazards of existence as their vital systems struggle to cope with an unfamiliar environment.

Many of these infants have trouble breathing, and their circulation is impaired. Because their livers and kidneys may be underdeveloped, they may have jaundice or acidosis. Their immature immunological mechanisms may leave them vulnerable to widespread infection, and the function of the digestive tract may be disorganized during adjustment. To add to their problems, the very methods that are used to treat them, such as oxygen supplementation, may create new hazards such as the risk of blindness.

Undoubtedly, it would have been far better if these new-

borns could have remained in the uterus longer. The long-run solution to the problems of such infants lies in finding ways to assure initiation of labor at the time of optimal intrauterine development. While such solutions are being sought, the management of these fragile newborns is receiving intensive study, in an effort to overcome many of the factors that threaten their survival. In this area, there has been slow, but gratifying progress.

The effects of environmental factors and maternal nutrition on the birth weight of newborns have been studied by an NICHD-supported investigator at Sinai Hospital in Baltimore, in collaboration with a team of Japanese obstetricians and pediatricians. In analyzing records covering the 20-year period after World War II, they found that the mean birth weight increased over prewar levels, with a striking increase in weights for the latter part of pregnancy, despite no increase in gestational age. These findings suggest that although there may be some genetic effects, socioeconomic factors such as improved economic and health conditions have been prominent in bringing about the change in birth weight. These studies suggest, as well, that as social conditions improve in the United States, some reduction in the number of low-birth-weight infants may be seen.

Other studies supported by the Institute have shown that newborn infants survive better if the environments in which they are raised make relatively small demands on their ability to regulate their body temperature. On the basis of animal experiments, it appears that temperature characteristics of the external environment affect both the growth and internal temperature regulation of newborns. Recent Institute-supported research has shown this to be true of humans as well. If small, healthy newborns spend two weeks in a relatively cool environment (95° F., compared with the normal incubator temperature of about 98.6° F. or higher), their cold resistance (the ability to prevent a fall in deep body temperature in an environment of 82.4° F.) is greater than that of infants kept in a warmer (about 98° F.) environment. However, the infants who had been in the cooler environment gain height and weight less rapidly. The investigator believes that these newborns may gain weight more slowly because they use relatively more of their caloric intake for heat energy, and less for fat storage than their warmer peers.

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INFANT MORTALITY IS HIGHER IN THE UNITED STATES THAN IN MANY OTHER MAJOR NATIONS



Some newborns with low birth weights have been found to have lower than normal blood sugar (hypoglycemia), a condition which, if left untreated, can cause severe brain damage and mental retardation. Recent Institute-supported studies have shown that this metabolic disturbance occurs frequently and primarily in twin pairs in which the smaller infant weighs less than four and one-half pounds. The investigators propose that the lower mental abilities often seen in the smaller of twins is caused by such hypoglycemia; they suggest that if frequent blood samples for glucose are taken, especially during the first 24 to 48 hours after birth, the problem can be prevented by glucose treatment.

Jaundice caused by hyperbilirubinemia is another problem of newborn infants that can lead to brain damage and retardation. Although treatment by exchange transfusions has been used for this condition, this is often as hazardous for premature infants, or more so, than the disorder itself. An NICHD-supported investigator at the University of Vermont has now confirmed that a surprisingly simple new method of prevention of hyperbilirubinemia is effective, particularly for premature babies. He has found that if newborns are exposed to long periods of artificial light, they do not develop hyperbilirubinemia. The basic mechanisms of light treatment, and improved applications of the technique, remain to be determined.

Respiratory Distress Syndrome

Mortality in the newborn period is highest among premature infants; most of those who die have signs of respiratory disease. For newborns whose deaths are attributed to the respiratory distress syndrome (RDS), it appears that a crucial process of adaptation of their lungs to the new extrauterine environment does not occur. Clues to the cause of this severe, often fatal, condition are being uncovered, but the problem is complex, and it is not yet clear whether one or several disease entities is involved in the syndrome.

One focus of NICHD-supported studies of RDS concerns the synthesis and nature of the pulmonary surfactant. This material, consisting largely of phospholipids, lubricates the surfaces of the lungs' air sacs and prevents their collapse; it is normally produced by the alveo-

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lar cells of the lungs once the human fetus has reached a birth weight of about 1,000 grams (or a little over two pounds). However, in infants who have died of respiratory distress attributed to hyaline membrane disease, the lungs are deficient in surfactant.

To establish the origins of the surfactant deficiency, Institute grantees and others have been exploring several related avenues. Studies of blood flow in the lungs of fetuses and newborns have suggested that bronchial blood flow significantly affects the synthesis of surfactant. According to NICHD-supported scientists at Columbia University studying neurophysiological factors underlying RDS, the stability of the alveolar cells and the production of surfactant depend on stimulation from the vagus nerve. All of these research findings are contributing to a new understanding of the respiratory distress syndrome, and will aid in the development of new techniques for reducing the number of newborn deaths.

Sudden Death Syndrome

Each year in the United States about 10 to 15 thousand apparently healthy infants, particularly those between the ages of two and six months, succumb to an unpredictable and mysterious condition known as the "Sudden Death of Infancy Syndrome." On autopsy, there seems to be no cause for the death. Infectious diseases had long been suspected to be a major contributing factor for several reasons: there are twice as many cases in winter as in summer, most cases occur in infants between five weeks and five months, when an infant may be particularly at risk to infectious agents. Suffocation has also been a suspected factor, but it fails to explain why very young infants are spared, why there are seasonal waves, or why associated infection is so often present.

Recently, a team of researchers in Seattle, Washington, has opened other areas of investigation. In their view, death in these cases is caused by a threshold phenomenon surrounding a minor infection. Although such infections might be innocuous in adults, in an infant they might act on the autonomic nervous system, causing the vocal cords to constrict. This, in turn, would close off the passage of air in the windpipe, and death would result from asphyxiation.

To gain more precise understanding of the conditions surrounding the sudden death syndrome, NICHD contracted with the Children's Hospital in Washington, D.C. for a study of unexpected infant death, emphasizing its correlation with upper respiratory viral infection. The investigation began as soon as possible after the death of the infant, and included not only cultures of the infant's body fluids for indications of viral infection, but also sputum and serum cultures from the family members. The investigators found that of the 58 children studied, 39 died of causes unexplained by autopsy. Of those, better than half had one or more viruses or bacteria present, and a high incidence of upper respiratory viral infection was found in them and in their families. From such studies, the cause, and eventually the prevention of this type of infant death will emerge.

Early Immunological Mechanisms

While in the uterus, the fetus exists in an environment that protects it from foreign proteins and some infectious agents, provided the natural body defenses of the mother and the placenta function adequately. However, from birth, the newborn infant enters a world filled with infectious organisms and foreign substances that his system must combat if he is to stay alive. Many factors, acting together, comprise this defense or immunological system to provide the protective responses necessary for survival. To understand better how these defenses work, studies of the development of this system and its basic mechanisms in the fetal, newborn, and infancy periods are supported by NICHD.

One study has demonstrated that highly developed immunological capacity exists in unborn and newborn infants, contrary to the assumption that the fetus has only poorly developed immunological capacities. Studies such as this continue to expand the understanding of the mechanisms underlying the development of immunities, and, together with other findings, may lead to revised notions of the ages at which children should be immunized.

Until recently, serum or circulating antibodies developed in response to infection had been considered to be most significant factors in resisting infectious disease. Thus, immunization programs have

been directed toward researchers have also known of the body—the tracts, the colostrum do not believe them to be absorbed by the body in production of antibodies in the tracts as a result of the presence of such local indicator of resistance against respiratory infection.

Studies of the immune system supported by the Institute of Medicine and bacterial antibodies in the intestine before birth produced in the external environment of the intestine. Further studies have shown to be more highly concentrated in the blood than in the tissues.

Another local site of infection is the kidneys. One investigator has found that the kidneys resisted infection in previously infected them, and that the levels of circulating antibodies were not caused by the local infection.

As a further study, it was found in the colostrum that four days after childbirth, antibodies from colostrum were found in infants, but not in those who had not also been shown to be in the intestinal tract than those who are protected from digestive role in resistance to infection. Further study.

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been directed toward improving this avenue of natural protection. Researchers have also known that antibodies exist in the external secretions of the body—the mucus of the respiratory and gastrointestinal tracts, the colostrum of the mother's milk, and the urine—but they did not believe them to be important, since these secretions were not absorbed by the body in large quantity. However, they now know that local production of antibodies apparently occurs in the cells lining these tracts as a result of natural or experimentally induced infections. The presence of such locally produced antibodies may prove to be a better indicator of resistance to infections and may provide greater protection against respiratory infection than circulating antibodies in the blood.

Studies of local immune systems are being increasingly supported by the Institute. One such study has already shown that viral and bacterial antibodies appear in feces and are associated with naturally occurring infections of the bowel. Since these antibodies appear in the intestine before they are seen in the blood, they seem to be produced in the external secretions after stimulation by an organism from the intestine. Further, resistance to intestinal infection has been shown to be more highly correlated with antibody levels in the intestines than in the bloodstream.

Another local immune system has been identified in rabbit kidneys. One investigator supported by NICHD has demonstrated that the kidneys resisted reinfection with the same organism that had previously infected them. Since this resistance was not related to high levels of circulating serum antibodies, the protection was presumed to be caused by the locally produced antibody of the urinary tract.

As a further example, local antibody production has been found in the colostrum—the secretion of the breasts for the first two to four days after childbirth, preceding the secretion of human milk. Antibodies from colostrum have been found in the feces of breast-fed infants, but not in those of formula-fed infants. These antibodies have also been shown to be more resistant to the acid and pepsin of the intestinal tract than those from the serum, suggesting that milk antibody is protected from digestion. If colostrum antibodies are found to play a role in resistance to diarrhea-causing organisms, the role of breast feeding as a means of preventing diarrhea in newborns will deserve further study.

Child Development: Normal and Abnormal

Assessing Individual Variations Through Growth Studies

Once a child survives the hazards of intrauterine life, the birth process, and the immediate adjustment to the world beyond the uterus, the Institute's areas of research emphasis shift from problems of immediate survival toward study of factors affecting the kind of person that infant will become. Will he fulfill the best potential of his particular genetic heritage, his familial and cultural background, and his individual physical, intellectual, and personality characteristics? The answer depends upon the unique genetic and environmental interactions that specify the unfolding of individual physical and psychological characteristics.

Recent research with both animals and humans has suggested that the nutritional, social, psychological, and other environmental events in early infancy and childhood have a profound effect on the course of subsequent development. Within this extraordinarily sensitive and impressionable stage of life, there are certain "critical periods" when children are particularly vulnerable. At these times, young-

ters may suffer environmental stressors. The Institute's research focuses on the timing and intensity of these environmental influences and stimulations and stimulates the critical periods.

To gain insight into the process, the Institute is developing a timetable of child development in identifying the process.

One of the major goals is to follow a group of children from birth to follow a group of them at regular intervals to see the way they develop and account for some of the problems that are gathered from the environment. It may be possible to identify individuals within a group in which some individuals have abnormal patterns of development or initial problems.

The Institute's research on nutritional and psychological factors produces both normal and abnormal patterns of individual development. The studies have the potential status as a model for the study of the next.

While the Institute's diverse research in the field of child development, California Institute of Technology, genetic, biological,

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ters may suffer lasting damage from too much or too little of certain environmental stimuli that at other times might have little effect. Thus, the Institute's research interests include study not only of the conditions and stimuli children need to help them grow normally, but also of the critical periods involved.

To gain some answers to these important basic questions, the Institute is particularly interested in descriptions of the normal timetable of child development, both physical and psychological, and in identifying those factors that accelerate, retard, or otherwise alter the process.

One of the best ways to study the course of development is to follow a group of children for many years, testing and measuring them at regular intervals to see both the similarities and differences in the way they change. Factors forming the background that might account for some of their differences may be documented. When data are gathered from a sufficiently large number of population groups, it may be possible to describe what is "normal" for certain types of individuals within a given group, and to identify, and even predict ways in which some individuals are, or will be, abnormal. Hopefully, if abnormal patterns of development are detected early enough, some potential problems might be prevented.

The Institute has given support to a number of cross-sectional and prospective, long-term growth studies. Cross-sectional studies produce both norms and comparisons at one time of differences among individuals at various ages. Prospective studies follow growth patterns of individuals. Both types of study are vital tools for identifying the ways in which children grow and develop. While cross-sectional studies have their value in the description of size, shape, and maturational status at a given age, longitudinal studies have proved uniquely suited for the assessment of changes that occur from one age to the next.

While no single project can be entirely representative of the Institute's diverse interests in human growth variability, one, the Oakland, California, "Child Health and Development Studies," is a characteristic example. This large-scale study is designed to investigate how genetic, biologic, medical, and environmental factors affect the out-

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come of pregnancy and the subsequent development of offspring. Its particular strength lies in the large number of families enrolled, and the similarity of the participant population to the general employed population of our country. In addition, unlike subjects in many other pregnancy outcome studies, women in this project generally enroll in the first trimester of pregnancy, thus permitting the entire prenatal period to be studied. To date, over 20,000 pregnancies have been followed, and nearly 18,700 live-born infants have entered the study. These investigations have included complete blood typing of families, studies of placentas, blood tests for viral diseases during pregnancy, and developmental studies on the majority of these children through five years of age.

Although the study is still incomplete, a number of interesting findings have already emerged. For example, it has revealed that patterns of morbidity and mortality among infants of low birth weight (3 lb. 5 oz. to 5 lb. 8 oz.) differ, depending upon their gestational age. Low-birth-weight infants who have grown relatively rapidly *in utero* and are born prematurely have difficulty in their immediate adaptation to extrauterine life. Infants who have grown relatively slowly *in utero*—being born at full term but with low birth weight—survive the first month of life well; however, they are subsequently more likely to show abnormalities and/or to be ill than those with more rapid intrauterine growth. By studying the effects of “overdue” pregnancies (those extending for more than three weeks beyond the expected delivery date), the investigators have found that in such cases, fetal and neonatal mortality rates were almost double those of normal pregnancies. The live-born infants were more likely to be severely ill during the first two years of life, but by five years of age, neither their growth nor their intelligence differed from that of children born after a more normal gestation period.

In contrast to the breadth of the Oakland study, with its focus on prenatal factors affecting subsequent development, other longitudinal growth and development studies supported by the Institute are aimed at more specific, limited targets such as cholesterol levels in the blood.

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create, in part, human diversity. For example, all children go through essentially the same growth processes, but with variations in their rates and time schedules. As a result of this, fast-growing children may be larger than slower growing children at one age, but at a later age, they may be the same size or even smaller. NICHD-supported longitudinal studies of child growth and development within the Institute and in such locations as Boston, Philadelphia, Nashville, Louisville, Ann Arbor, Denver, and Portland have yielded considerable information on growth patterns in white and black populations.

In one study, an Institute staff member gathered data concerning the growth of urban North American black schoolchildren over a 78-year period. He has found that on the average, urban 14-year-old blacks are gaining more in height every 10 years than their white classmates in Canada and the United States. This height gain resulted largely from an increase in leg length, not torso length. The study also showed that the weight of these black schoolchildren has been increasing relatively more rapidly than their height. Improved nutritional conditions may account for some of these changes.

Some of these examples of growth studies help to clarify the relative roles of genetic and environmental influences in shaping growth patterns, and aid in defining how such indicators of biological age as bone formation and the appearance of secondary sexual characteristics are related to chronologic age.

Noteworthy progress has also been made in several projects dealing with variability in the growth of certain organs such as the lungs, skeletal muscle, kidneys, and brain. These studies have contributed fundamental knowledge concerning the intimate relationships between the forms and functions of organs in children of different ages, whether healthy or ill. Other projects have led to a better understanding of the development of the skull and face, and the disturbances that may arise as a result of endocrine and metabolic disorders. The increased availability of such longitudinal research data has set the stage for the development of improved techniques for predicting normal and abnormal growth. Pediatricians, surgeons, and orthodontists are thus gaining more sensitive methods for detecting and dealing with cases of apparently deviant growth. These efforts hopefully lead to the

Biological Growth and Health

Hormonal and Metabolic Factors

Since its inception, NICHD has supported a large number of research projects related to biological maturation after birth, many of which are concerned with how growth is regulated by the endocrine glands (organs which internally secrete substances that affect the function of other organs). Primary areas of study concern the effects of the various hormones on growth and organ function, the mechanisms underlying these effects, and the changes in hormone production that occur during different periods of growth.

Currently, the availability of human growth hormone (which is obtained solely from the human pituitary), is severely limited. To meet the demand for the hormone as a therapeutic agent, Institute-supported scientists, among others, are trying to characterize it chemically so that a synthetic hormone can be made widely available. Other scientists have demonstrated that various fragments of the growth hor-

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mone molecule have unique biological effects; these findings may lead to simplified production of biologically active material for clinical use. Investigators are also trying to purify the growth hormone from animals, and are observing its effect in patients. New methods currently being developed to improve measurement of this hormone in body fluids will simplify the diagnosis and therapy of abnormal growth, and contribute to the understanding of normal growth.

Studies of the factors that control growth hormone release from the pituitary gland have been particularly interesting and productive. One source of control, the hypothalamus (a portion of the brain that controls many important biological drives such as thirst, hunger, fear, and sex) appears to be especially important. Extracts from the hypothalamus have been shown to cause the pituitary gland to release growth hormone. In rats, this effect varies with age, being more pronounced in the young, growing animal. When some of the hypothalamic tissue is destroyed in animals, their growth rate is reduced, and the amount of growth hormone in the pituitary gland and the blood is changed. The structure of the pituitary gland itself is also altered after hypothalamic damage. The interrelation between the hypothalamus and the release of pituitary growth hormone has also been shown by a more positive method: when the hypothalamus is stimulated electrically, growth hormone may be released from the pituitary gland.

These findings suggest several new avenues for clinical studies aimed at correcting retarded growth in children. A number of investigators are studying children with growth retardation to determine whether they have pituitary malfunction, and to see whether growth hormone might help them. Investigators in one clinic have studied a group of severely emotionally deprived children whose physical growth was retarded. Their findings suggest that such psychological deprivation may actually suppress pituitary function and inhibit the release of growth hormone. This study provides insight into the intimate connection between physical and emotional factors in both healthy and abnormal child development.

Through other studies that have produced and standardized techniques for studying hormone metabolism in infants and children, patterns of normal and abnormal hormone secretion rates throughout

childhood are being established. Hormonal secretion rates during adolescence have been examined with particular attention, for hormonal changes occur rapidly as the patterns of childhood shift to those of adulthood. One study has established the secretory pattern of the pituitary hormones that stimulate production of sex hormones in children undergoing both normal, delayed, and advanced sexual development.

Many Institute-supported investigations of the biology of maturation are concerned with the study of growth at the cellular and molecular levels. Research is being conducted on the synthesis and structure of the substances that comprise living matter such as protein. Cell growth and multiplication, the role of enzyme systems in growth, tissue synthesis and regeneration, metabolic processes, and other basic problems related to growth are being studied as well.

An interesting project at The Johns Hopkins University has been devoted to studying the growth of muscle cells in normal children, in those with retarded growth from various causes, and in those showing "recovery" growth after heart surgery for congenital heart disease. Muscular growth after birth appears to be associated mainly with an increase in the size of muscle cells, rather than in their number. Poor nutrition chiefly affects the growth of the size of the muscle cells (resulting in small cells that are nonetheless normal in number), whereas conditions such as pituitary insufficiency and primordial dwarfism produce a deficiency in cell number. Sex differences in muscle growth have also been more clearly defined by this study. Girls' muscle cells increase in number at a constant rate (linearly) over time as they mature; they show their full muscle cell size by about age 11. By contrast, in boys, an increase in muscle cell size continues beyond 11 (to an age yet unknown); during adolescence their cell numbers increase exponentially—that is, at an ever-increasing rate.

Another aspect of the same study has shown amino acid metabolism to be an important factor in children's growth. In children whose growth has been retarded, amino acid levels may be lower than normal both in the blood and muscle cells; when growth hormone is given to children with malfunctioning pituitary glands, amino acid concentrations are increased. Amino acid concentrations were also found



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The Institute has given support to a number of cross-sectional and prospective, long-term growth studies. Cross-sectional studies produce both norms and comparisons at one time of differences among individuals at various ages. Prospective studies follow growth patterns of individuals. Both types of study are vital tools for identifying the ways in which children grow and develop. While cross-sectional studies have their value in the description of size, shape, and maturational status at a given age, longitudinal studies have proved uniquely suited for the assessment of changes that occur from one age to the next.

While no single project can be entirely representative of the Institute's diverse interests in human growth variability, one, the Oakland, California, "Child Health and Development Studies," is a characteristic example. This large-scale study is designed to investigate how genetic, biologic, medical, and environmental factors affect the outcome of pregnancy and the subsequent development of offspring. Its

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Study of another aspect of metabolism, has been made possible by the development of a new research technique available, using a radioisotope of calcium has been used to study both normal children and those with

Nutritional Factors

Nutrition is of fundamental importance in the developing child. The nutrients in food are the building blocks for bones, muscle, and organs. When the body achieves its genetic potential, the nutrients in food are used to maintain the organs, thereby controlling the rate of growth. It is increasingly apparent that the effects of malnutrition will adversely affect the child's physical size, organ function, and mental development. Similarly, overnutrition in the adult can lead to obesity, with its own set of biological and physical hazards. Research is being conducted to understand the factors that lead to abnormal nutrition. Research is also being conducted on the ecological factors associated with the effects of behavior and environment on nutrition.

In this section of the report, the physical growth will be examined in relation to proper and improper diet with particular emphasis on the sequential effects of children's nutrition on both physical and intellectual development in ways that are just becoming

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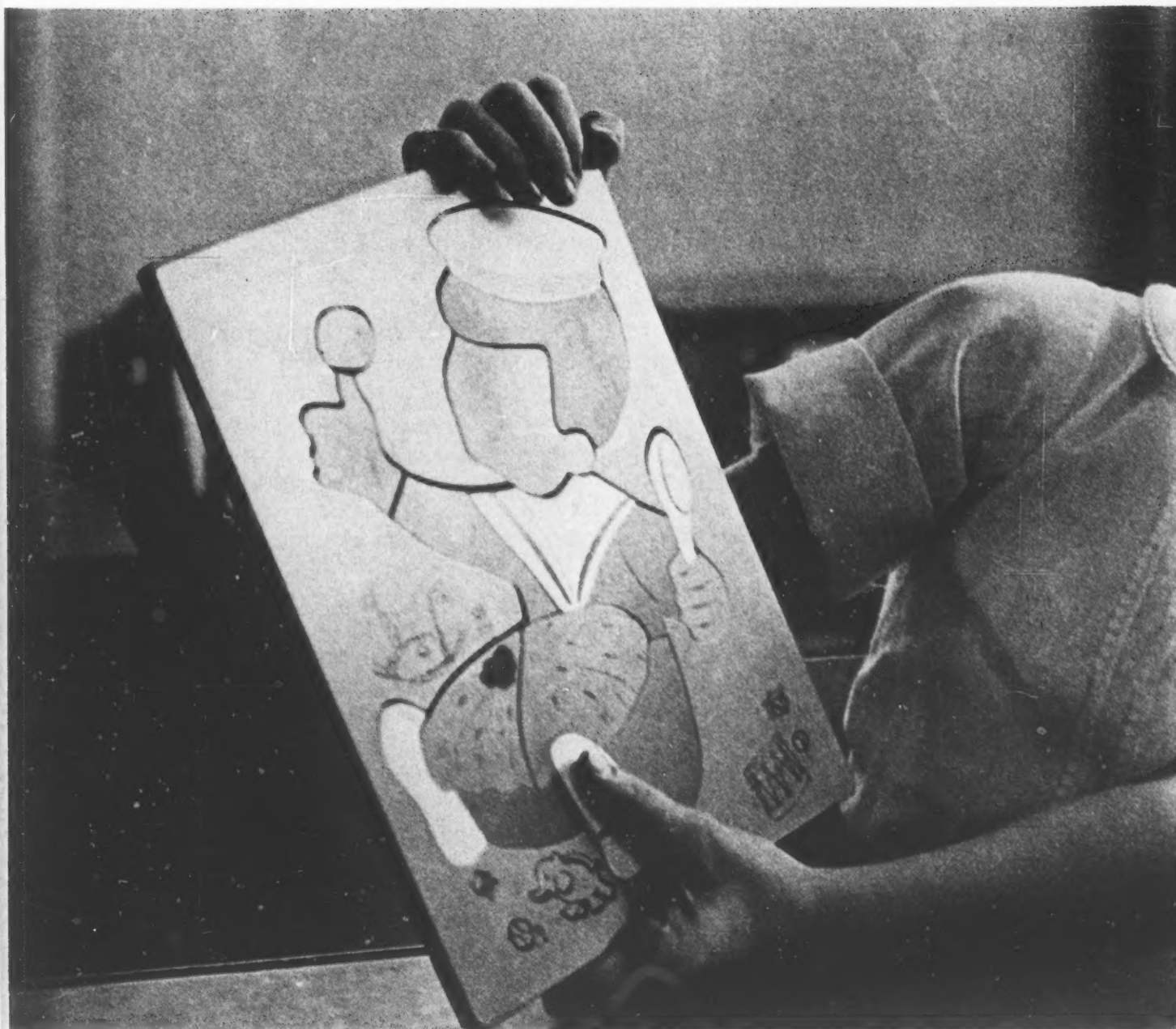
to increase normally during adolescent growth.

Study of another aspect of child growth, namely calcium metabolism, has been made possible through the Institute-supported development of a new research technique. Until now, normal calcium metabolism in children was difficult to study because the most accurate technique available, using radioactive calcium, exposed children to the risks of radiation. Recently, however, a stable, nonradioactive isotope of calcium has been developed which should aid in studying both normal children and those with bone diseases.

Nutritional Factors

Nutrition is of fundamental importance to the growing, developing child. The nutrients contained in food provide the building blocks for bones, muscle, and fat, thereby determining whether the body achieves its genetic potential in size and shape. More importantly, the nutrients in food influence the development of cells and organs, thereby controlling their functional capacity throughout life. It is increasingly apparent that there are critical periods in development when malnutrition will adversely affect growth, possibly irreversibly. Physical size, organ function, and perhaps mental development may be impaired. Similarly, overnutrition in childhood can lead to permanent adult obesity, with its own well-known cluster of related psychological and physical hazards. The nutrition area of interest of NICHD is centered on understanding the effects of under- and overnutrition so that they can be prevented or overcome. The program is directed toward the behavioral as well as the biological aspects of normal and abnormal nutrition. Research is being supported on the social and ecological factors associated with food practices and behavior, as well as the effects of behavior and/or emotional patterns on nutrient utilization.

In this section of the report, the effects of nutrition on physical growth will be examined, while the intellectual implications of proper and improper diet will be discussed later. In fact, the consequential effects of children's pre- and postnatal nutritional intake on both physical and intellectual growth are intimately interrelated, in ways that are just becoming understood.





One of the most exciting fields in nutrition research is the area of cell development. For years, malnutrition in infancy or childhood has been known to produce permanent effects on growth, depending on the organ under study, the type of dietary stress imposed, and the age of the subject. Now, scientists are beginning to understand why. The growing mammal undergoes continuous change in metabolism, form, and function. At specific periods in time, certain proteins must be manufactured to become part of cells and enzyme systems. Simultaneously, previously needed proteins disappear to become still other cell components. The patterns differ from cell to cell, from tissue to tissue. The process is closely orchestrated so that failure of one step, through lack of necessary nutrients, upsets the scheme and permanently alters the process.

Recent studies may have laid the foundation for the control and prevention of at least one example of a nutritional problem—obesity—and may contribute to understanding the basic response of cells to a variety of nutritional conditions. Using both animals and human tissue samples, one investigator has shown that increased intake of protein or amino acids influences the secretion of insulin, resulting in an increase in the size of muscle cells. If caloric intake is increased, growth hormone secretion is influenced, causing an increase in cell number, rather than size.

By observing the growth of fat tissue in animals and in humans, two other investigators have found that early nutritional factors, such as overfeeding, appear to produce obesity by permanently increasing the number of fat cells. In the normal human, the number of fat cells has been shown to increase up to about one year of age, whereas the increase in cell size occurs up to age six, continuing at a lower rate until at least puberty. One of these scientists has observed a marked increase in the total number of fat cells, as well as an increase in cell size, in extremely obese adults who had been fat for a long time. When these individuals lost weight, cell size was diminished while cell number remained constant. Tissue samples from adults who had become obese experimentally—prison volunteers eating a high calorie diet—showed an increase in cell size, but not in number. Taken

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together, these findings suggest that obesity starting early in life, perhaps in infancy, may be associated with an increase in cell number, whereas obesity starting later in life occurs via increase in cell size with no effect on cell number. These two patterns may require entirely different preventive and therapeutic approaches. Inasmuch as one-sixth of all Americans may be classified as suffering from obesity, which predisposes them to chronic diseases such as high blood pressure, diabetes, arteriosclerosis, and certain kidney diseases, this approach to understanding the origin and nature of obesity assumes great health significance.

The behavioral approach to the problem of obesity has also been taken by Institute-supported scientists. In a University of California study of eating habits and attitudes, about 1,000 teen-agers were studied as they progressed from the 9th through the 12th grades. Although only 11 percent were found to have "excess" body fat, 60 percent thought they should lose weight. The study also confirmed that teen-agers do not get enough exercise. Throughout the study, the youngsters showed a continuing high level of interest in their body conformation and in methods to make it more ideal. The study provides a wealth of specific information about behavior patterns that could serve as a basis for workable programs of weight control and physical fitness for teen-agers.

Intellectual and Social Development

From its beginnings, NICHD has had a commitment to study the development of man's special faculty—his extraordinary intellect—and to find new ways to overcome adverse factors that may prevent some from fulfillment of his best intellectual potential. As with a child's physical development, the growth of his mental capabilities begins with the genetic factors he inherited from generations before him. They are then molded, sometimes irrevocably, by the nutritional, metabolic, chemical, and physical forces of his prenatal environment; are profoundly affected by the events immediately surrounding his birth and adjustment to postnatal existence; and thereafter depend upon how the sum of all these experiences interacts with a lifetime of con-

tacts with the nutritional and environmental conditions, diseases, experiences, and people that make up his world. These developmental conditions are being studied with an eye toward their relative contributions to normal and abnormal intellectual growth. Particular attention is being given to identifying critical stages at which interventions might enhance the capacities of the individual, or reverse or prevent damage caused during earlier stages.

Some of the basic genetic and intrauterine conditions affecting mental development already have been discussed. This section will deal primarily with the postnatal events that shape the mental skills of infants and children as they face increasing demands upon their abilities to perceive, to reason, and to communicate. It will stress efforts to overcome the special problems of the poor, who, as noted earlier, often suffer from a constellation of conditions which hamper the full development of their physical and mental capacities.

Nutrition and Mental Development

Scientists have long known that nutritional deficiencies, whether based on inadequate total food intake or lack of individual nutrients, could retard physical growth and delay sexual maturation. Within recent years, the possibility of an additional hazard has caused concern: malnutrition during intrauterine life, early infancy, and childhood may impair mental as well as physical development.

The results of experiments in animals are clear and dramatic: body and brain growth can be slowed, and behavioral patterns and learning ability can be impaired by severe malnutrition. The kinds of disabilities produced, the degree of severity, and reversibility depend upon the types of malnutrition imposed, the length of the deprivation period, and the developmental stage at which malnutrition occurs.

The developmental timetable of the particular animal under study also determines the effects seen, since animal species differ in relative rates of brain development before and after birth. For example, the guinea pig brain develops primarily before birth (prenatal brain development), the rat brain develops mainly after birth (postnatal brain

development), and human brain development occurs during pregnancy and the first three years of life. In the human, the growth period for the brain is nearly complete at birth. In many species, mental development is nearly complete at birth. In some species, mental development is nearly complete at birth, but intellectual development continues throughout fetal and postnatal life.

According to a recent report, 10 million babies in the United States in the first three years of life have permanent mental retardation. These statistics are based on a portion of the population.

Unfortunately, many of these children are in this area. In animal experiments, undernourished animals, however biologically, do not reach the intellectual capabilities nor the social problem concepts of man. From the social point of view, there is usually a sufficient amount of food to affect intellectual development.

To get a better understanding of the effects of malnutrition on the development of human populations, the National Institute of Child Health and Human Development (NICHD) has been studying the effects of malnutrition on the development of human populations. In Guatemala, in a large proportion of the population, there is a deficiency of food and

mental conditions, diseases, exist in this world. These developmental factors tend toward their relative contribution to individual growth. Particular attention is given to the stages at which interventions can be made, individual, or reverse or prevent the effects of intrauterine conditions affected have been discussed. This section will discuss factors that shape the mental skills of children by placing demands upon their ability to learn and communicate. It will stress efforts to improve the lives of the poor, who, as noted earlier, often live in conditions which hamper the full development of their capacities.

that nutritional deficiencies, inadequate intake or lack of individual nutrients, and delay sexual maturation. An additional hazard has caused by malnutrition in early life, early infancy, and childhood development.

In animals are clear and demonstrated, and behavioral patterns are affected by severe malnutrition. The kinds of malnutrition, the severity, and reversibility determined by the length of the deprivation, the stage at which malnutrition occurs, and the particular animal under study.

of the particular animal under study, since animal species differ in their development before and after birth. For example, in man, before birth (prenatal brain development) and after birth (postnatal brain

development), and the pig brain develops during the last trimester of pregnancy and in early infancy (perinatal brain development). The human brain, like that of the pig, develops perinatally; its greatest growth period takes place around the time of birth, tapering off until it is nearly complete by two years of age. Since the susceptibility of each species to mental impairment through malnutrition seems to be greatest during the period of rapid brain development, for optimal human intellectual development adequate nutrition is clearly essential throughout fetal development and the child's first two years.

According to United Nations statistics, over half of the 116 million babies born annually in the world are undernourished during the first three years of life. If it is shown that the effects of malnutrition permanently interfere with a child's ability to learn and think, these statistics suggest that the mental development of a significant portion of the human population may be impaired.

Unfortunately, extrapolation from animal experiments to humans in this area is extremely difficult. The dietary restrictions used in animal experiments are frequently more severe than those existent in undernourished human populations. Further, the animals studied, however biologically similar to man, do not share the sensitivity and reach of man's intellect; they can show neither the range of man's abilities nor the subtle impairments to which he is susceptible. Another problem concerns the seeming inseparability of malnutrition in man from the social context in which it occurs. Where malnutrition exists, there is usually also a social environment that alone would be sufficient to affect intellectual development adversely.

To gain greater insight into the meaning of malnutrition for man, NICHD has been supporting both animal experiments concerning the effects of malnutrition on critical developmental stages, and studies of human populations suffering from severe malnutrition. Major attention is being given to the latter studies. The most carefully designed of these, aimed at analytically separating social factors from nutritional factors affecting intellectual development, is being conducted in Guatemala. In that country, as in many other developing nations, a large proportion of children die before they are five, because of insufficient food and lack of medical care; those who do live are often se-

verely stunted for life. Eighty-five percent of all Guatemalan children under six are significantly underweight, 90 babies per 1,000 die in the first year of life, and life expectancy is under 50 years.

The Guatemalan study, conducted by the Institute for Nutrition of Central America and Panama, is a long-term, intensive field investigation of the relation between nutritional status and the physical, psychological, and social development of children. Four rural isolated villages, each with about 650 inhabitants, have been paired and matched as closely as possible according to their social, economic, medical, nutritional, and child developmental characteristics. All villages have received medical care not previously available, but in only one village of each pair has a nutritionally adequate supplement been provided systematically to all pregnant women and to children. (In the villages receiving no supplement, children who are found to be suffering from severe malnutrition are rehabilitated and followed as a special group within the study.) In all the villages, both mothers and their offspring are being repeatedly studied for medical, nutritional, and social factors by an interdisciplinary team of researchers. In addition, all children are to be followed for psychological development until they reach the age of seven. At that age, any differences in mental development, if they occur, should be apparent.

Preliminary results of the study have confirmed that marked nutritional deficiencies exist in the pregnant women and the young children in these villages, reflected in abnormal placentas, in poor physical growth of youngsters, and in related high mortality rates. To study the differences in mental development and behavior among the experimental and control subjects, the investigators have refined existing psychological and social tests, and have new ones, designed to uncover and measure any adverse effects of malnutrition. They have confirmed that children rehabilitated after severe malnutrition do not perform as well on some psychological tests as their brothers and sisters who had never been malnourished. This finding suggests that severe malnutrition itself, rather than the adverse social environment, may be associated with deficits in intellectual development.

Many other projects bearing on the relation of nutrition and intellectual development are also under way. In one study, the differ-

ences between intellectual development of malnourished and well-nourished siblings are observed. Research is being pursued with a view to determining the reversibility and permanence of the damage.

Early Experience and Nervous System

A broad program of research is being conducted to determine how early experience affects development and behavior. Special studies are being made in impoverished environments to determine the effects on intellectual abilities.

It is known from studies of institutionalized children that early in the life of young organisms, experience has a profound effect on subsequent behavior. Researchers are studying the physiological changes underlying these effects.

Two investigators have studied the quality of animals' early experience versus group rearing, or being reared in isolation, and the result later in differences in behavior, stress, and in their general health. These findings suggest that early experience radically alters typical aggressive behavior. Similar studies of other species are being conducted to spread such findings among the general public.

The other investigators are studying the critical periods in which certain experiences permanently structure the nervous system and the resulting behavior. It is believed that certain emotional traits can be passed on to successive generations because of the interaction of the environment with their offspring.

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ences between intellectual development of malnourished and normally
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search is being pursued with animal models to define better the nature
and permanence of the damage to the central nervous system.

Early Experience and Nervous System Development

A broad program of research is being supported by NICHD to
determine how early experience affects central nervous system devel-
opment and behavior. Special attention is being given to the effects of
impoverished environments upon development, particularly of social
and intellectual abilities.

It is known from both animal experiments and clinical stud-
ies of institutionalized children that a lack of adequate social contact
early in the life of young organisms can have lasting effects on subse-
quent behavior. Researchers are beginning to find out more about the
physiological changes underlying such effects.

Two investigators have demonstrated that variations in the
quality of animals' early experience—such as being raised in isolation
versus group rearing, or being handled versus nonhandling—can re-
sult later in differences in individuals' adrenal gland response to
stress, and in their general emotional responses. One of these re-
searchers has demonstrated that, unlike normally reared mice, those
reared with rat mothers are not spontaneously aggressive toward rats.
These findings suggest that certain common early experiences may
radically alter typical aggressive behaviors in some animal species.
Similar studies of other species will be needed to determine how wide-
spread such findings are among animals.

The other investigator has proposed that there may be criti-
cal periods in which certain neuroendocrinological and hormonal fac-
tors permanently structure and organize the developing nervous sys-
tem and the resulting behavior patterns. Thus, as his data suggest, cer-
tain emotional traits can be passed along by behavioral factors through
successive generations because of the built-in ways in which mothers
interact with their offspring.

One intrinsic hormonal and behavioral mechanism of mam-

In assessing the impact of early experiences on behavior, another productive approach is to study how brain chemistry and structure are affected by such events. Recent experiments by one NICHD-supported investigator have begun to pinpoint the impact of environmental stimulation on brain development. These studies have shown that when animals are reared in isolation, there are significant reductions in the number of cells in the cortex, cerebellum, and limbic systems of the brain. The investigator has also found that if social isolation is imposed early in development, the subcortical brain structures (which mature early) are impaired, whereas if isolation is begun later in life, cell loss occurs in the cortical brain structures (which develop later). Since emotion and behavior are associated with subcortical structures, and intellectual development with cortical structures, these findings suggest also that early isolation brings on emotional and behavioral abnormalities, while later isolation impairs intellectual capacity. This investigator has also demonstrated that animals reared in isolation metabolize certain neurochemical substances faster than group-reared animals; these differences are related to the increased activity and aggressiveness of those isolated. These neurochemical findings complement those from neuroendocrinological research concerning adrenal responses to stress following isolation.

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At a time when efforts are being directed to the safety of children from violence, it is recognized a special effort provides extensive information on aspects of the legal system. In such efforts, it is important to bring a sound scientific approach. It should also suggest intellectual skills.

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and their offspring is the male animals show a 50% reduction in situations when they are the moderator of the mother's behavior. In turn protects the changes in maternal be-

experiences on behavior, new brain chemistry and recent experiments by one group pinpoint the impact of environment. These studies have shown, there are significant changes in the cerebellum, and limbic system. They found that if social isolation is begun in subcortical brain structures (which are associated with subcortical structures), it brings on emotional and behavioral impairments. Intellectual development is retarded in animals reared in isolation. These neurochemical and physiological research conclusions.

He found that light deprivation in animals, particularly rabbits, in the visual cortex (the area of vision). His finding suggests that light deprivation during development in turn lead to learning-

described here are ob-

viously not applicable to the study of developing brain processes in the human child. Electrophysiological measures of brain function are thus among the preferred tools for studying and evaluating how impoverished environments and psychosocial deprivation affect brain development in children. A number of electrophysiological studies of brain function are being supported by the Institute. They are providing basic data on the development of neuroelectric processes of the brain, and are particularly directed toward determining whether certain EEG "brain signatures" can be identified that are characteristic of impaired brain function which could result from early nutritional or psychological deprivation.

In an exciting new discovery, one investigator has found, and another has independently validated, the existence of EEG patterns that are characteristic of high and low intelligence. Dull normal subjects (average IQ = 80) do not have significant differences in the electrical activity of the two halves (hemispheres) of their brains whereas, bright normal children (average IQ = 140) do show significant differences. This research, which shows that direct measures of intellectual capacity can be related to neural functioning, is being extended to other human groups to determine whether a critical period exists for the development of this brain characteristic.

Overcoming Learning Disabilities

At a time when widespread new educational programs are being developed and introduced throughout the United States, and efforts are being directed particularly toward improving the learning ability of children from disadvantaged backgrounds, the Institute has recognized a special responsibility to parents and educators alike. It provides extensive support for studies that may illuminate fundamental aspects of the learning and communicative processes in children. By such efforts, it is hoped that the Institute may contribute to establishing a sound scientific basis for educational policy. Such research should also suggest new techniques for enhancing the acquisition of intellectual skills by the Nation's children.

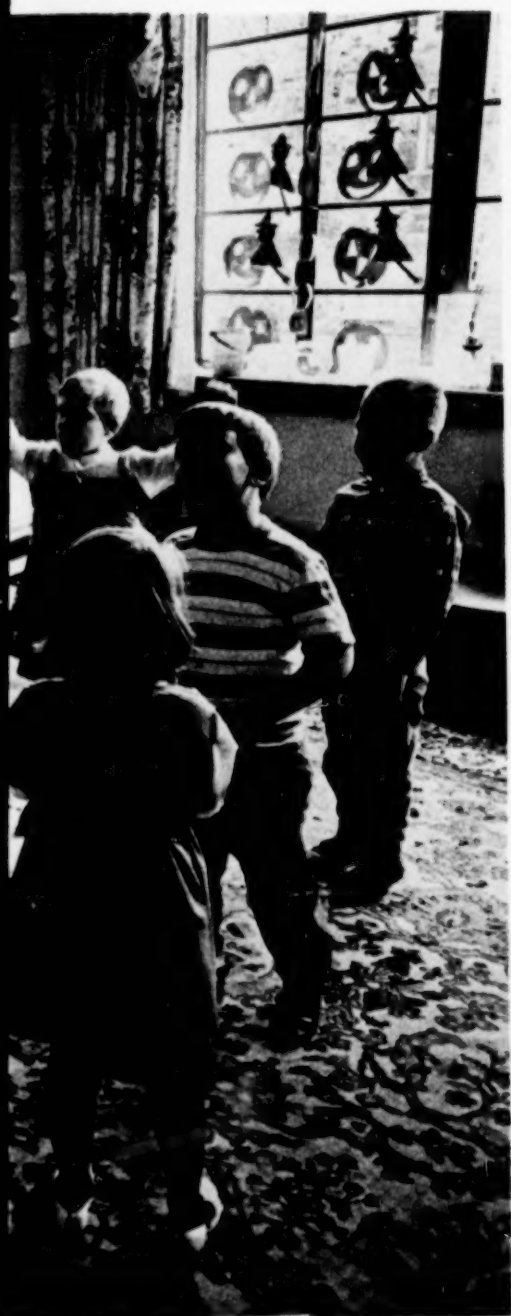
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study of learning; it has included investigations of the capacities and motivations of individuals; the basic mechanisms of acquiring, storing, and retrieving information; and the personality and social variables that affect the entire learning process. Support has been given not only to psychological and physiological studies (the traditional approaches to the learning process), but also to investigations of genetic and biochemical aspects of learning at the cellular and molecular levels. Efforts to understand the normal learning process have been complemented by studies of ways to prevent or overcome impaired learning ability. Special attention has been given to determining the age or ages at which an intellectual deficit becomes permanent, and to developing tests that can predict and evaluate improvement in learning ability as new training techniques are applied.

In an attempt to understand the normal process of intellectual development in children, an investigator at the University of Colorado has been studying how cognitive behavior develops in preschool and school-age children, particularly how their approach to problem-solving shifts from dependence on seeing and manipulating concrete stimuli, to more abstract kinds of reasoning. He has found that when learning to solve problems, preschoolers have more difficulty than kindergarten children in overcoming an initial inappropriate response tendency (they prefer to respond to the location of stimuli rather than to characteristics more relevant to solving the problems). Second graders do not seem to have this response tendency. Although the preschool, kindergarten and second-grade children differ significantly in their ability to verbalize solutions to problems, and appear to use different problem-solving strategies, their achievements are essentially similar.

Several studies within the Institute have attempted to pinpoint the specific time in the developmental pattern when children from deprived environments first show specific intellectual and social deficits. They have also sought to identify the environmental factors that create or can overcome such impairments. In one study, researchers are comparing how early maternal stimulation affects the exploratory behavior and intellectual functioning of six-month-old infants from lower- and middle-class backgrounds. The behavior patterns of the two

Under an NICHD contract, an investigator at Harvard University has conducted a longitudinal study of how differences in the child-rearing techniques of women of various classes affect their children's intellectual development during the first three years of life. After observing children of lower- and middle-class families at the ages of four, eight, 13, and 27 months, his preliminary findings revealed that significant class differences in the development of attention are

Many studies have shown that positive reinforcement can improve the IQ of children, especially those who are at risk of being labeled as "learning disabled." As the child grows older, the reinforcement can be more specific, such as praise for good behavior or for completing a task. Parents have been able to overcome the negative effects of poverty and poor nutrition on children's IQ by using positive reinforcement and lesson kits. For example, a study of "privileged" children, and by using positive reinforcement to encourage progress through praise and encouragement. Through this technique, children could not resist nagging from their parents or teachers. The investigators

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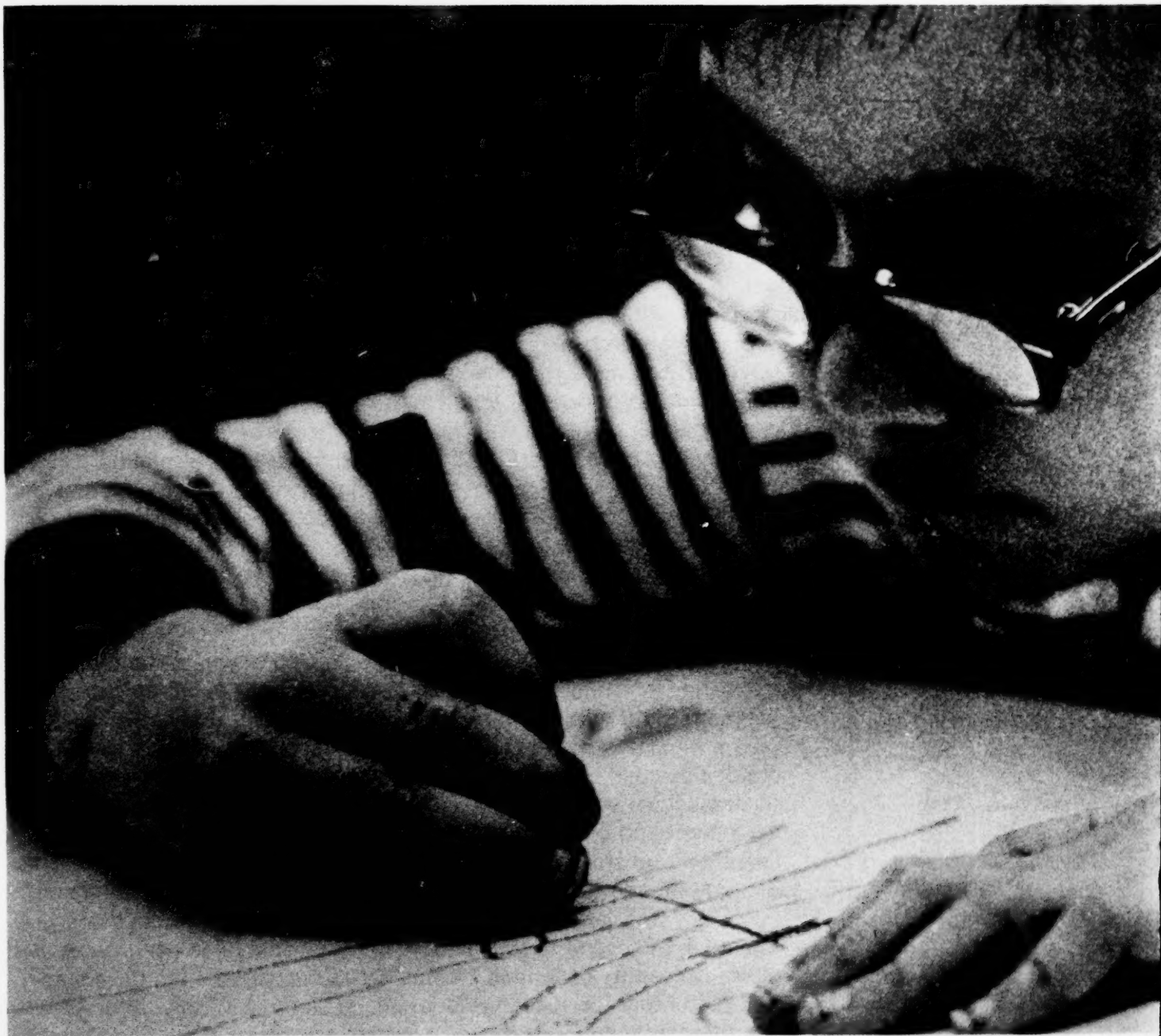
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already evident by four months of age, and are greater for girls than for boys. By this age, differences in the infants' responses to distorted pictures of faces (as measured by decreases in their heart rates) indicated that upper-middle-class infants are more clearly sensitive to such facial distortions than are lower-class infants. These differences are thought to be related to the amount of face-to-face contact between the infants and their mothers. Class differences were also found in the response of eight-month-old infants to their mothers' leaving the room. Lower-class infants are less likely to burst into tears immediately than their middle-class peers; presumably, they suffer less from separation anxiety, or are not so dependent upon their mothers.

A team of NICHD investigators is evaluating the effectiveness of preschool learning programs such as Head Start, which have been established to provide special learning experiences for children from deprived environments. These scientists are trying to gain more precise information concerning the kinds of learning conditions that promote the development of cognitive skills in young children, and motivate children to want to learn. The first phase of research has concentrated on creating methods for measuring the types of controls and rewards teachers use to encourage children's mental skills, the ways that children's language and conceptual skills develop, the capacity of children to concentrate and control impulsive behavior, and the views children have of themselves and others. Tests developed by the investigators to evaluate the intellectual development of these preschool children have already proved to be valuable in predicting their learning capacity and relating their social environment to school readiness.

Many studies have demonstrated that while preschool education can improve the IQ scores of children, these gains are not sustained as the child grows older. Investigators at the University of Kansas have been able to overcome some of this "slippage" by giving instruction and lesson kits to mothers of mildly retarded "culturally deprived" children, and by guiding them to reinforce their children's progress through praise and encouragement. The success achieved through this technique was enhanced by having the mothers (who could not resist nagging their own children) teach children other than their own. The investigators in this program believe that parent-child







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teaching and training may help to break the self-perpetuating cycle of cultural deprivation.

To improve the educational motivation of deprived older children, the same Kansas City investigators have used remedial instruction courses in which incentive points are given for doing homework and for grades earned in regular school classes. The points can then be traded in for daily snacks, field trips, picnics, toys, or clothing when enough are accumulated. During the first year of this program, the pupils from a sixth-grade remedial class showed significant academic progress; their grade average was raised from D to C, and yearly gains on public school achievement tests more than doubled. The same researchers ran a similar remedial classroom for junior high drop-outs who belonged to the local neighborhood Youth Corps. These students were paid for each problem worked correctly in class. Within two months, their achievement test scores improved significantly more than those of peers working at regular jobs and not attending classes.

Among the basic skills children need for intellectual and social growth is competence in the communication arts of reading, writing, and speaking. An important goal of the Institute is therefore aimed at improving "normal" reading and language skills, and eliminating reading and other communication problems through fundamental research into the nature of these processes.

Intrafamily relationships are particularly important in the socialization of children and in the acquisition of communication and language skills. Studies supported by the Institute indicate that in deprived families, there is limited verbal interaction between parent and child. The style of communication in such homes is poor preparation for the school setting or for daily problem-solving. Since language development and communication are indispensable to learning, other researchers are studying the processes involved in learning and communication in order to modify and advance the retarded child's skills.

One large research project supported by the Institute is illustrative of several in this area. A five-year study has been conducted at the University of Oregon Medical School to explore the development and maturation of speech and language skills in young children. With the Institute's support, the researchers are now completing the crea-

tion of a standardized test of selected communicative skills. The test will enable diagnosticians and therapists to have much better criteria for determining whether a given child is developing atypically or "within normal limits" as his language ability expands.

Since learning depends greatly on sensory and motor input, these systems must be sound to assure an effective learning experience. In school, many children are slow learners because of sensory and motor defects. For example, children with cerebral palsy may not do well in school because of their poor coordination. While completely blind, deaf, or mute children have their handicaps recognized and, hopefully, compensated for in the school environment, those with partial or subtle impairments of sight, hearing, or speech may have their learning difficulties inappropriately attributed to limited intellectual ability or lack of effort. Investigators in New York City have developed a series of tests aimed at helping to recognize partial impairments affecting learning. These tests check the children's auditory-visual, visual-touch, and visual-motor activities, and their ability to integrate these important faculties. Through these tests, one group of investigators has shown that reading disabilities often reflect an interference with auditory-visual interaction, although this may not be the sole factor in their disability. They note that this type of sensory integration in its more complex and general form may be one process underlying adaptive behavior and IQ; individuals who can perceive and integrate many sensations such as touch, vision, and hearing are likely to be the more intelligent ones. This continuing research is based on the principle that each sensory system in the body interacts with and is modified by other sensory systems, and that even the simplest sensory function is modified by activity in other senses. The investigators believe that in humans, such sensory integration is a developmental process that follows a definite age and growth curve.

Institute-supported researchers of the George Peabody College for Teachers, in Nashville, have been studying how the motivation of mentally retarded individuals affects the vigor with which they perform simple motor tasks. Subjects were asked to punch as many holes as they could in a specially prepared answer sheet within a short time period. At the conclusion of each of four trials, they received either a

penny, a dime, no reward, or no reward. The results showed that subjects who were motivated by a reward (pretesting to achieve their performance of tasks) performed better than they did under money contrast, extrinsically motivated subjects performed best when paid. The results also showed motivational characteristics signing educational and wo

The Child's Social Growth

The development of people around them begins and continues through their early years until they finally become adults. The Institute supports studies beginning with the infant's first cooperation with NIMH on stranger anxiety in infancy and spontaneous fear in nine-month-old middle-class children. The social stimulation they receive is ample, infants who receive social stimulation (through the mother) to ensure extensive eye-to-eye contact with strangers than those given less. The frequency of eye-to-eye contact of age appeared to determine how they approach strangers, and how they react when held by them. The commonly measured crying of infants' reactions to stranger behavior of fathers significant attachment of their infants

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penny, a dime, no reward, or another, more interesting job. The study showed that subjects who were intrinsically motivated (those shown by pretesting to achieve their main satisfaction through the actual performance of tasks) performed better under the promise of another task than they did under money-reward or no-reward conditions. By contrast, extrinsically motivated subjects (whose main satisfaction comes from the comfort, security, and material rewards of the environment) performed best when paid. These findings suggest that personality and motivational characteristics of retardates should be recognized in designing educational and work settings and reward systems for them.

The Child's Social Growth

The development of children's responses to the world of people around them begins as soon as infants open their eyes, and continues through their encounters with family, friends, and school-mates until they finally become full-fledged members of their culture. The Institute supports studies of the entire socialization process, beginning with the infant's first visual behavior. In a study carried out in cooperation with NIMH on the development of social attachments and stranger anxiety in infancy, NICHD scientists have found that stranger anxiety and spontaneous friendly behavior on the part of the eight- and nine-month-old middle-class infants is correlated with the kinds of social stimulation they received at one to three months of age. For example, infants who received higher levels of auditory and visual stimulation (through the mother's talking or singing or positioning the baby to ensure extensive eye-to-eye contact) were significantly less afraid of strangers than those given less of this kind of stimulation. The frequency of eye-to-eye contact between mother and baby at one month of age appeared to determine which boys would spontaneously approach strangers, and how much they would look directly at strangers' faces when held by them. Thus, visual behavior (as well as the more commonly measured crying and protest) is a sensitive indicator of infants' reactions to strangers. The investigators have also found that the behavior of fathers significantly affects the age of onset and degree of attachment of their infants toward them. For boys, the more their fath-

ers took care of them and played with them, the more attached they grew. Such findings should contribute toward more solid understanding of children's earliest social development.

Another investigator is also studying how parents influence their children's social development. Using interviews and questionnaires, he is trying to determine the extent to which parents influence high school and college students in the areas of career planning, school, heterosexual activities, and grooming. Since parental influence on adolescents is a form of social power, this investigator is attempting to distinguish the types of power parents can exert, such as coercion or rewards, and the extent to which they use their power.

The influence of parental attitudes and behavior on the development of mentally handicapped children has been recognized by investigators at the NICHD Children's Diagnostic and Study Branch, who are studying the effects of diagnostic counseling on the parents of retarded children. They have been observing how parents' views of their children's current behavior and their future expectations for them are changed by such counseling. This research is based on the premise that a retarded child's parents can manage him better and plan for his future more accurately if they are given all necessary diagnostic, prognostic, and program information available regarding their child. To date, several trends have emerged from this study. Although parents usually estimate accurately their child's present abilities, they are poor in estimating his future social adaptability. Parents who are inaccurate in estimating current abilities are less successful in managing their child than those whose assessments are accurate. Parents often see their child's difficulties as the sum of many separate little problems—such as poor speech or poor motor coordination—which are amenable to therapy; counselors sometimes reinforce this erroneous view. In general, contact with the diagnostic clinic usually makes parents more realistic about their children; the degree to which their views change depends upon the physician's strategy of counseling.

Major research interest also exists in the area of the development of values, attitudes, judgments, and behaviors. Such development appears to follow a specific pattern: children pass through definite stages in a specific chronological order, although, since children

vary in their rate, they undergo similar stages. Children's attitudes and values are influenced by their parents' attitudes and values—but may also be influenced by the school, as well as with the peer group. Reported investigations of children's values and attitudes show that views of children's school to senior high school are found to be similar. Developmental areas are family and friends, attitudes, and personality. These are expected to be related to the extent to which the child's attitudes, parental understanding, and the child's own understanding.

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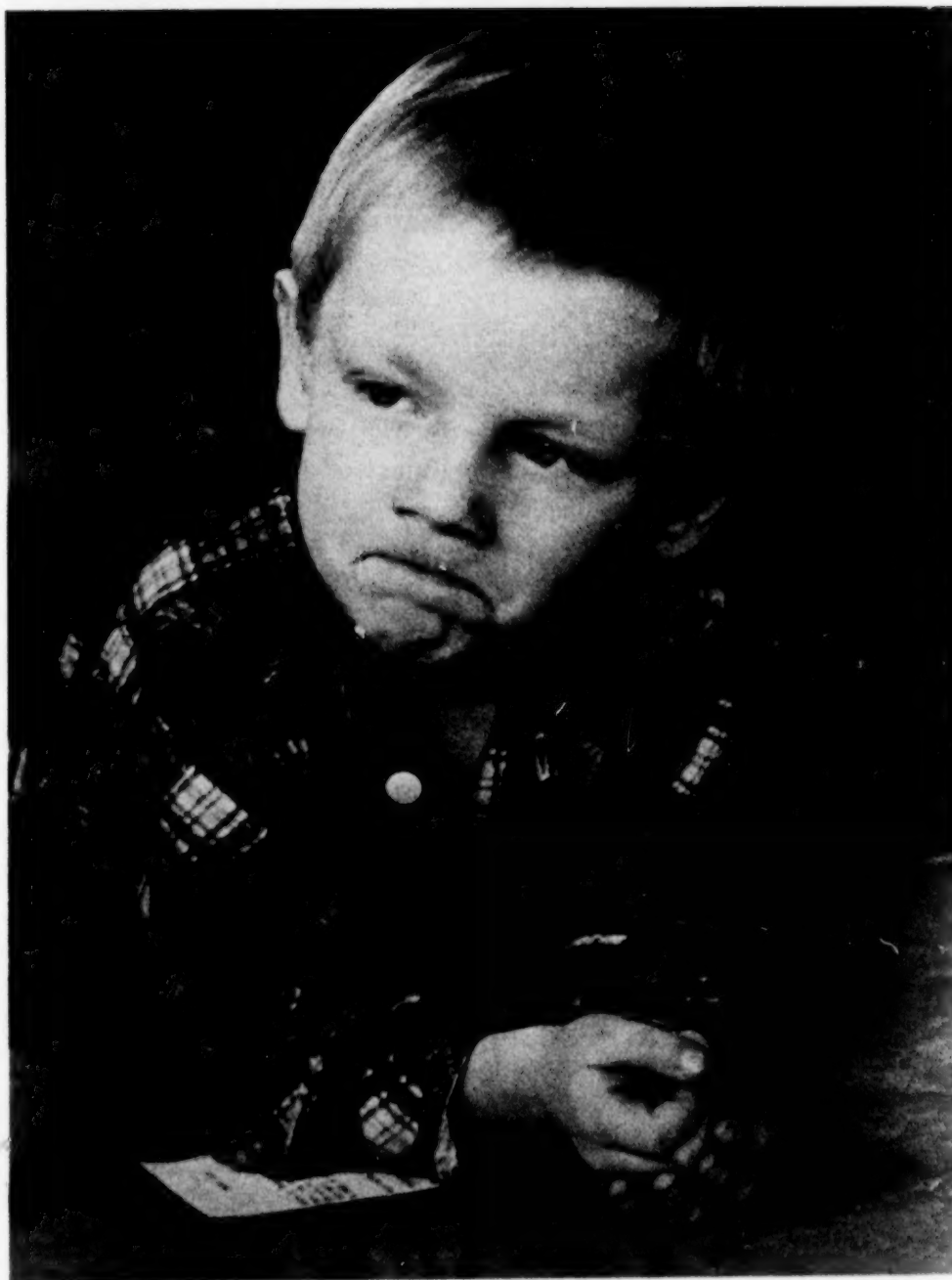
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vary in their rate of development, they may differ in the ages at which they undergo specific stages. The influence of parents on their children's attitudes, judgments, and behaviors may occur through the children's identification with their parents—their wish to be like their parents—but may vary with the support and warmth the parents provide, as well as with specific parental disciplinary styles. One NICHD-supported investigator is assessing intellectual and behavioral aspects of children's value development using several types of tests and interviews of children in five different age groups, ranging from nursery school to senior high school. The social backgrounds of groups of children found to be particularly high or low in various aspects of such development are studied closely and are compared. Of particular interest are family and parent-child relations, the parents' own behavior and attitudes, and parental communication and teaching. Studies such as these are expected to yield important information on the relative extent to which the development of values depends on child-rearing practices, parental example, and specific teaching. They should also aid in understanding the factors underlying personality development.

Parents are by no means the only source of socialization in the modern world. Perhaps the most important nonparental socializing force for the young child is his school. Two important studies of the relation between the child and the school are currently in progress. One of these is concerned with how a child's performance when he enters school is affected by the interaction of his attitudes with those of his teacher—especially if the child is a member of a minority group. This important project is developing significant new attitude measures for use among children in the lower elementary grades. These tools will aid in determining children's views of segregation and desegregation, as well as their reactions to the school system and the learning process itself.

A second, longitudinal, study is exploring the long-term psychological and scholastic effects of desegregation on a group of California schoolchildren. Begun in the 1965-66 school year (one year prior to desegregation of the public schools in Riverside, California), the project has documented subsequent changes in the academic achievement and emotional adjustment of approximately 1,800 children who



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were originally in the kindergarten through the sixth grades of black, Mexican-American, or white schools. Some preliminary comparisons of the three groups' characteristics before and soon after desegregation (utilizing bussing) are readily available. For example, when shown pictures of racial stereotypes prior to desegregation, and asked to pick the person "most like me," approximately 80 percent of the white children, 56 percent of the black children, and 48 percent of the Mexican-American children chose pictures of their own ethnic group. With increasing age, minority group children were more likely to view their ethnic identity accurately, while for white children, the reverse was true. Pre- and postdesegregation comparisons suggest that integration accentuates the racial awareness of all the children, particularly those in the minority groups; after integration, the latter are more likely to choose members of their own ethnic group as one they would "most like to be" or would "most like as a friend."

When members of the three student groups were given a simple ring-toss test and their levels of expected achievement and actual performance, as well as their reactions to success and failure were compared, the Mexican-Americans proved to be the most competent on the test, and had the most realistic expectations; white subjects overestimated the most, and had the lowest actual scores. After desegregation, these ethnic group differences decreased.

These results, and others yet to emerge from the project, are expected to provide a large body of information on the characteristics of black, white, and Mexican-American children of various social classes and ages, and should aid other schools attempting to set guidelines for desegregation.

The Riverside desegregation study, which takes advantage of opportunities to observe social changes as they occur, represents a direction of NICHD programming which is being given increasing emphasis. Five years ago, NICHD supported very few projects concerned with personality development and social growth in children. Today, about 30 grants are concerned generally with the parent and child in modern society, reflecting both active staff programming and the increasing awareness by behavioral scientists of NICHD's interests in supporting dynamic studies of this kind.

The Reproductive Process: Basic Biology and Its Relation to Family Planning

When a young person reaches the age of sexual maturity, his social, psychological, and biological roles change significantly. He not only feels the difference himself, but his society, regardless of its location or level of sophistication, usually recognizes the difference through special rituals, ceremonies, and celebrations that mark his entrance into the adult world.

His newly acquired reproductive capacity makes him no longer simply the product of an ancient biological and social heritage; he now becomes the potential creator of another generation of humans. He becomes a source of immortality for himself, his family and culture, and the species. His creative potential, however, is a two-edged sword.

Each child who comes into the world is at once a possible source of enrichment for all mankind, and a threat to the well-being of all others who share his need for food, space, air, water, and the tech-

nological and social resources of the world. If the biological and social resources were adequate for all, the attitude that the consequences of the act of conceiving them. Unfettered population is increasing (it appears that by the end of this century) such a situation is not afforded. Voluntary limitation of reproduction is but imperative.

NICHD recognizes the need for research toward understanding the basic biology of fertility and sterility, the long-term effects of reproduction on health, the biological bases of fertility, psychological, and social-group factors in population dynamics.

The Institute is exerting leadership coordinated by the Department of Health and Human Services, National Advisory Child Health Council, in promoting:

"... the day when each parent will be able to control the number of children. Each fertilized egg will have a chance to develop into a physically and mentally healthy newborn infant with the opportunity for survival and reproductive maturity."

NICHD has been developing research within the Federal Government studying not only the biological bases of fertility and fertility, but also the psychological and social factors with which they are related. One aspect of the program is being devoted to understanding how individuals

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nological and social resources of his community. If the supply of these resources were adequate for all men, it might be possible to afford the attitude that the consequences of producing children are as private as the act of conceiving them. Unfortunately, at the rate the world's population is increasing (it appears that if present growth rates continue, three and one-half billion humans will double to over seven billion by the end of this century) such a narrow perspective can no longer be afforded. Voluntary limitation of family size is not only advantageous, but imperative.

NICHD recognizes this fact, and is directing intensive efforts toward understanding the basic biological processes involved in fertility and sterility, the long-term effects of current contraceptive methods on health, the biological bases for new methods, and the behavioral, psychological, and social-group factors involved in family planning and population dynamics.

The Institute is exerting every effort to fulfill the goal, enunciated by the Department of Health, Education, and Welfare, and the National Advisory Child Health and Human Development Council, of promoting:

"... the day when each child is wanted, when parents will be able to exercise free choice as to the number of children they wish to have, when each fertilized egg will have the greatest possible chance to develop into an infant that will be born physically and mentally normal, and when each newborn infant will have the greatest possible opportunity for surviving and developing to productive maturity."

NICHD has been designated as the focal point for population research within the Federal Government. It is deeply committed to studying not only the biological and medical aspects of reproduction and fertility, but also the psychological, socioeconomic, and cultural factors with which they are intertwined. This behavioral research aspect of the program is being given increasing emphasis as a key to understanding how individuals might be motivated to reduce the size

of their families, and as a means of revealing how economic development and population size, growth, and distribution are interrelated. Such research knowledge may eventually serve as a basis for population policy and action programs in the United States and abroad.

Menstruation and Ovulation

For many girls, the beginning of menstruation marks their entry into womanhood. From that day (generally in their 12th or 13th year) until they reach menopause (usually in the middle to late 40's), they will undergo the relatively regular monthly cycle through which their reproductive system repeatedly matures new eggs and provides a rich, nutrient environment within which fertilized eggs can mature. Within the monthly cycle, the fertility of women varies. A peak is reached around the time of ovulation, about in the middle of the monthly cycle. For any program directed toward understanding and controlling human fertility, the nature of the female menstrual cycle is a prime target of study, particularly the events surrounding and controlling ovulation.

To obtain a definitive description of how the menstrual cycle varies from woman to woman, and within the same woman as she develops from menarche to menopause, the Institute is supporting the continuation and extension of a longitudinal study of women's menstrual histories begun in 1934 at the University of Minnesota. After studying more than 22,000 woman-years of menstrual experience, the investigators are now sure that the 28-day cycle presumed to be characteristic of most women is a myth. There is generally great variation in cycle length among women, and for each individual, the seven earliest and latest years in the reproduction cycle are usually marked by particularly variable cycles. Even during the relatively stable years of the middle to late 30's, there is a gradual drop in menstrual-cycle interval of two or three days. These findings suggest that the body's rhythm is not sufficiently regular and predictable to make simple calendar counting an effective basis for the "rhythm" method of birth control.

The study also revealed that mothers and their daughters do not necessarily have menstrual cycles of the same length, even when they are compared at identical ages; in general, the daughters showed



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far greater variability. The lengths of the first pregnancies of mothers and daughters also did not correlate well.

While the menstrual cycle is easy to document, the pattern of ovulation in women is extremely difficult to discern accurately. Scientists are looking for a reliable and simple indicator of the time of ovulation so that ovulatory physiology and chemistry can be more readily studied, and techniques both for overcoming infertility and controlling conception can be made more effective.

Working with rhesus monkeys, whose reproductive physiology is very much like that of humans, a group of researchers has suggested that the amount of estrogen excreted in the urine during the menstrual cycle may provide an accurate means of predicting when ovulation will occur. Their preliminary results show that just before the expected time of ovulation, there is a peak in urinary estrone. In most subjects, ovulation occurs within two days, and is correlated with a marked reduction in estrogen excretion. When there is no ovulation, the estrogen levels remain low throughout the menstrual cycle. These findings may contribute to a fast and easy urine test to predict and record the exact time of ovulation in humans.

Sperm Capacitation

Since the early 1950's, scientists have known that freshly ejaculated sperm are ineffective in fertilizing eggs of many mammals. The sperm must first undergo a process of capacitation (or maturation), in many experimental animals, if fertilization is to take place. The capacitation process, which occurs in the uterus and oviduct of the female, appears to involve the removal of a decapacitation factor naturally present in sperm. An Institute grantee at the University of Georgia has been purifying and characterizing this factor in seminal fluid of rabbits and bulls as preparation for the synthesis of this natural substance to control sperm efficacy. If the capacitation-decapacitation process is found to occur in primates, use of a decapacitation factor could provide the basis for a new contraceptive method; the reproductive power of human sperm could be inhibited at will, then reversed when children are wanted.

Cervical and Oviduct Function

When the sperm reach the egg, there are many physical and biochemical changes that progress toward the egg. Many clues are emerging from Institute-sponsored research, both therapy for infertility and on prevention of pregnancy.

The role of the cervix, the gateway to the uterus, is under particular scrutiny. It is known that there are biochemical changes in the mucus of the cervix during specific phases of the menstrual cycle. The mucus becomes more creases progressively before ovulation. After ovulation, that at ovulation it is quite abundant (during the phase of the corpus luteum), and then it dries up. We have also found that the fluid mucus is more watery during ovulation, while viscous mucus has the effect of preventing fertility control measures has thus far been unsuccessful.

Another approach to the problem of sperm in the female has been taken by Dr. Robert L. B. By studying women with infertility, he has found that the cause could be found, he and his colleagues have found that a large percentage of the women had antibodies to their husbands' sperm. Apparently, the sperm were inactivated, and had developed immune responses to inactivated sperm in their reproductive tract. New ways of overcoming this allergic reaction are an additional route for the control of fertility.

Important early events in the process of sperm penetration of the ovum, oocyte, and the oviduct has different effects on the sperm, permitting the former to ascend the tube. It seems likely that by interfering with the mucus (hairs) lining the tube, or the non-mucus lining of the oviduct, fertilization can be prevented. We are exploring this avenue as well.

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Cervical and Oviduct Function

When the sperm reach the female reproductive tract, there are many physical and biochemical events that aid or impede their progress toward the egg. Many clues to understanding these events, emerging from Institute-sponsored research, promise to shed light on both therapy for infertility and on potential birth control methods.

The role of the cervix, the neck of the uterus, has come under particular scrutiny. It is known that physical, and possibly biochemical, changes in the mucous lining of the cervix accompany specific phases of the menstrual cycle. The amount of mucus increases progressively before ovulation (during the follicular phase), so that at ovulation it is quite abundant and fluid. After ovulation (during the phase of the corpus luteum), it is scanty and jellylike. Scientists have also found that the fluid mucus helps sperm movement and survival, while viscous mucus has the opposite effect. Another target for fertility control measures has thus been identified.

Another approach to the biochemistry of fertility and sterility in the female has been taken by an investigator at Baylor University. By studying women with infertility problems for which no organic cause could be found, he and his co-workers discovered that a remarkable percentage of the women had antibodies in their bloodstreams to their husbands' sperm. Apparently, they had become allergic to the sperm, and had developed immunological responses that essentially inactivated sperm in their reproductive tracts. This study may lead to new ways of overcoming this allergic type of sterility, while suggesting an additional route for the control of fertilization.

Important early events in the reproductive process, such as sperm penetration of the ovum, occur in the female oviduct. For example, the oviduct has different effects on the sperm and the ovum, permitting the former to ascend the tube while the latter descends. It seems likely that by interfering with the tube's musculature, the cilia (hairs) lining the tube, or the normal composition of fluid in the oviduct, fertilization can be prevented. Institute-sponsored scientists are exploring this avenue as well.

Hormonal Control of Fertility: The Role of the Corpus Luteum

The events of the menstrual cycle occur through a precise meshing of self-regulating hormonal controls exerted by three main participants: the ovaries, the uterus, and the pituitary gland. There are two major phases to the cycle. During the follicular (preovulatory) phase, which extends for about nine days after menstruation stops, the wall of the uterus begins to build up, under the stimulation of the follicular hormone estrogen, secreted by the ovaries. Close to the 14th day of the cycle, ovulation takes place and an egg is released from the ovaries. At the same time, the concentration of estrogen in the blood reaches its peak, and the corpus luteum, vital for the next phase, begins to develop in the ovaries, under the influence of luteinizing hormone from the pituitary gland.

During the luteal (postovulatory) phase, estrogen in the blood decreases, and the corpus luteum becomes active and secretes progesterone. The primary function of this hormone appears to be to prepare the uterus for pregnancy and to maintain it during the early months of prenatal development. If conception does not occur, the corpus luteum changes and the concentration of both estrogen and progesterone in the blood falls sharply until a portion of the uterine wall is sloughed off through menstruation, and the cycle begins anew.

There is considerable research interest in the role of the corpus luteum in the reproductive cycle, since it seems to control the receptiveness of the uterus to implantation of the fertilized egg. Study of this phase of the cycle is expected to reveal ways to aid in the maintenance of early pregnancy (and thus prevent spontaneous abortions) as well as ways to prevent implantation. In some animal species, there appears to be a chemical agent naturally produced by the uterus which, if administered at the proper time, will cause the corpus luteum to regress as if fertilization had not occurred. It might therefore be possible to develop a medication that a woman could take at the time of her expected period that would physiologically inhibit the action of the corpus luteum and bring on menstruation. This approach to contraception is particularly appealing, since it would require a woman to take a pill only once a month.



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Family Planning

Assessment of Current Birth Control Practices

The ideal contraceptive, in the view of most family planning organizations, is effective, safe, inexpensive, reversible, and acceptable to various population groups. Thus, it must satisfy not only medical criteria, but economic and social-psychological criteria as well. Of the techniques now available, none fulfills all these conditions. Since no single method will be universally satisfactory in all situations, the Institute supports research that may lead to an array of methods more closely approaching the ideal than those now available.

The search for a biological basis for developing new contraceptives has been described on the preceding pages. NICHD also supports the evaluation of those methods already developed so that the patterns and consequences of their use can be understood and modified.

In many parts of the world, abortion is the leading method of birth control. Even in the United States, where, until recently, it has been generally illegal except when necessary to save the woman's life, as many as one million women a year are estimated to have had abortions, mostly illegally. Recognizing the significance of this controversial social phenomenon, the Institute has held the first federally sponsored workshops on abortion to explore current problems and gaps in knowledge. At these interdisciplinary meetings, participants identified high-priority areas for future study which encompassed the medical, legal, psychosocial, and epidemiologic aspects of abortion. Workshops such as these should serve to stimulate needed research concerning a significant social phenomenon affecting the well-being of many women and their children, and influencing profoundly the size of the world population.

Among the most common in the United States, the oral contraceptives (IUD's) have received particular support from scientists. Both methods represent advanced contraceptive technology; in many cases, they are the first choice for certain women. The Institute's support has focused on research to improve their use.

To understand the pattern of contraceptive use in the United States, the Institute gave a contract to Princeton University for a national survey of American family planning practices. The survey was conducted, on the basis of a sample of approximately 6.4 million women, of those who had used contraceptives at one time or another, and of those who expect to use them in the future. (The survey included American women, and 10 million women in other countries.) The survey findings are being used to evaluate the use of the pill at any time since its use, either permanently or temporarily. They had continued its use for at least one year. They were older women, those with fewer children, and those with the least education. Most of the women reported the effects of the drug (mainly either weight gain, or associated with pregnancy, or premenstrual syndrome). They tended to return to the pill, although some switched to other methods.

Findings gathered by the Minnesota menarche history study of oral contraceptive pill users in the United States show that most half, have discontinued the pill. One-quarter of the discontinuance was for medical reasons. Of 1,000 medical reasons, 206 reported "unwelcome disturbing effects," which comprised 20 percent of the discontinuance, from irritability to severe depression. More frequently than expected, as were the women who stopped the treatment to have a child, they returned relatively soon. Only one unwanted pregnancy in the contraceptive program was followed by a miscarriage.

Despite the widespread use of oral contraceptives, which are relatively new, and their long-term effects are still being studied. In 1967, Congress allocated funds for research on the medical effects of oral contraceptives. The Institute for this purpose.

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Among the most commonly used methods of birth control in the United States, the oral steroids ("the pill") and intrauterine devices (IUD's) have received particular attention from Institute-supported scientists. Both methods represent remarkable improvements in contraceptive technology; in many respects, they are the techniques of choice for certain women. They are both far from ideal, however, and Institute support has focused on assessing in great detail all aspects of their use.

To understand the patterns of actual and expected contraceptive use in the United States, particularly oral contraceptives, the Institute gave a contract to Princeton University to conduct a survey of American family planning practices. This National Fertility Study indicated, on the basis of a sample of 4,810 wives under age 45, that approximately 6.4 million women in the United States have used oral contraceptives at one time or another, and that another 4.7 million expect to use them in the future. (It is estimated that about 8.5 million American women, and 10 million in other countries are now using this method.) The survey findings also showed that of all women who had used the pill at any time since 1960, about one-third had discontinued its use, either permanently or temporarily, by 1965. About 85 percent had continued its use for at least one year. The "dropouts" tended to be older women, those with fewer than three children, and those with the least education. Most of them stopped because of unpleasant side effects of the drug (mainly either undesirable reactions commonly associated with pregnancy, or problems connected with the menstrual cycle). They tended to return to the contraceptive method used before the pill, although some switched or reverted to the IUD or foam.

Findings gathered by Institute scientists as part of the Minnesota menstrual history study mentioned earlier revealed that of 800 contraceptive pill users in the menstrual history program, 394, or almost half, have discontinued the pills for various reasons. Just over one-quarter of the discontinuances were for side effects, or for other medical reasons. Of 1,000 medical reports from pill users in 1966-67, 206 reported unwelcome disturbances such as "break-through bleeding," which comprised 20 percent of those disturbances. Psychic reactions, from irritability to severe depression, were reported more frequently than expected, as were impairments of sight. Most subjects who stopped the treatment to become pregnant were successful relatively soon. Only one unwanted pregnancy occurred when the contraceptive program was followed strictly.

Despite the widespread use of oral contraceptives, they are relatively new, and their long-term effects are not well known. Since 1967, Congress allocated funds specifically to support study of the medical effects of oral contraceptives; five contracts are sponsored by the Institute for this purpose.





The largest of these, with the Kaiser Foundation Research Institute in California, is a long-term study comparing the medical effects of oral contraceptives with other birth control methods used by women. Special examinations are conducted of over 20,000 women, some of whom are expected to be taking oral contraceptives, and some using other forms of contraception. When the study is complete, it should provide data on both biological and behavioral problems associated with the use of the contraceptives, and should clarify whether, over time, the use of oral contraceptives is related, for example, to cancer of the breast or cervix.

Among the other contracts, one was designed to help resolve the controversial question of whether the use of oral contraceptives affects the occurrence of cervical dysplasia, a pathological condition that can lead to cervical cancer. Another study, at the University of London, is devoted to evaluating the significance of documented changes in glucose and lipid metabolism produced by oral contraceptives. Preliminary results of the London study confirm that the use of oral contraceptives is associated with impaired glucose tolerance, even though fasting glucose levels are normal. This finding suggests that a mild form of diabetes may occur in women taking the pill. Many more subjects will have to be studied over long time periods to discover which factors, such as obesity, family history of diabetes, and the type and duration of contraception, are associated with the observed changes.

Studies in Great Britain have indicated that women who use oral contraceptives have an increased incidence of clotting and blockage of blood vessels (thromboembolic disease). In particular, the risk of death from pulmonary embolism or cerebral thrombosis is estimated to be seven to eight times higher in such women than in women not using the pills. This finding has been validated through a statistical study of mortality rates conducted by an NICHD scientist.

At an Institute-sponsored workshop held in 1968, 55 leading investigators reviewed and evaluated current knowledge concerning the metabolic effects of sex hormones and contraceptive steroids. Contributors revealed that contraceptive drugs produce widespread metabolic effects, leaving no tissue or organ system free from a biological, functional, and/or morphological change. Although most of the effects are reversible, they do challenge the body's physiological reserves, and in some women, the effects become prominent. The seriousness of such changes, particularly among long-term users of the drugs, remains largely to be evaluated.

Taken together, these findings mean that additional long-term work is needed to elucidate how oral contraceptives affect women and their children. Although for many women this contraceptive technique is the best available (and its risks may outweigh those of child-

bearing), for others, different methods are needed.

The second major area of research through Institute support is the mechanism of action of the IUD. Studies have begun to clarify the mechanism. Some investigators have found that when these foreign bodies block the fallopian tubes, that, by this local action, they prevent fertilization.

An Institute grant is also being used to study the effects of IUDs on estrous ewes. The results of these studies are being compared with sperm transport studies in humans. The mechanism of action of the IUD raised the question of the effectiveness of the IUD in humans. Agents such as sperm or bacteria are being studied.

A study of the effectiveness of the IUD in humans is being conducted in California, under an NICHD grant. The study is based on approximately 9,000 women who have had IUD insertions and surveys of their attitudes and experiences. The study will also include a survey of patient experience. Women who are the best candidates for the IUD, their attitudes, and their social and cultural factors are being studied.

Social, Psychological, and Cultural Factors in IUD Acceptance and Population Control

When the ideal of population control is not diminished by the world's population, it is not to accept them, and to understand the need for knowledge concerning the public's perceptions and acts (namely, the total population size) is a major effort by the Institute.

Although the Institute is relatively new, there are already a number of National Fertility Surveys which are a rich source of information on the United States. The investigators have noted that women interviewed in 1968 wanted relatively large families. The investigators have noted:

with the Kaiser Foundation Research
form study comparing the medical ef-
fects of other birth control methods used by
women. The study is complete, it
has been conducted of over 20,000 women,
taking oral contraceptives, and some
on. When the study is complete, it
will clarify the medical and behavioral problems asso-
ciated with oral contraceptives, and should clarify whether,
the use of oral contraceptives is related, for example, to

effects, one was designed to help resolve
whether the use of oral contraceptives af-
fects the incidence of cervical dysplasia, a pathological condition
of the cervix. Another study, at the University of
California, is studying the significance of documented
diabetes mellitus produced by oral contracep-
tion. A London study confirms that the use of
oral contraceptives in women with impaired glucose tolerance, even
when blood sugar is normal. This finding suggests that a
small percentage of women taking the pill. Many more
studies are being conducted over long time periods to discover
whether there is a family history of diabetes, and the type
of diabetes are associated with the observed

have indicated that women who use
oral contraceptives have a decreased incidence of clotting and block-
age of blood vessels (cardiovascular disease). In particular, the risk
of heart or cerebral thrombosis is estimated
to be higher in such women than in women not
taking oral contraceptives. This has not been validated through a statistical
study by an NICHD scientist.

A workshop held in 1968, 55 leading
scientists presented current knowledge concerning
the effects of oral contraceptives and contraceptive steroids. Con-
traceptive drugs produce widespread meta-
bolic changes in the body's organ system free from a biological,
chemical, or physical change. Although most of the effects
are on the body's physiological reserves, and
some are prominent. The seriousness of
the effects of long-term users of the drugs, re-

These findings mean that additional long-
term studies are needed to show how oral contraceptives affect women
and whether the benefits of this contraceptive tech-
nique outweigh the risks of child-

bearing), for others, different, and possibly as yet undiscovered, meth-
ods are needed.

The second major method of contraception receiving study
through Institute support is the intrauterine device. Although the
mechanism of action of the IUD is not well understood, recent animal
studies have begun to clarify its effects. Within the Institute, two scien-
tists have found that when IUD's were used in adult female monkeys,
these foreign bodies blocked the formation of the placenta. It appears
that, by this local action, the implantation of the fertilized egg is pre-
vented.

An Institute grantee in Maryland has shown that when IUD's
were used in estrous ewes, the devices inhibited fertilization by inter-
fering with sperm transport, apparently by reversing the normal direc-
tion of uterine contractions. This investigator also found that the pres-
ence of the IUD raised the inflammatory reaction of the uterus, so that
agents such as sperm or bacteria were readily killed.

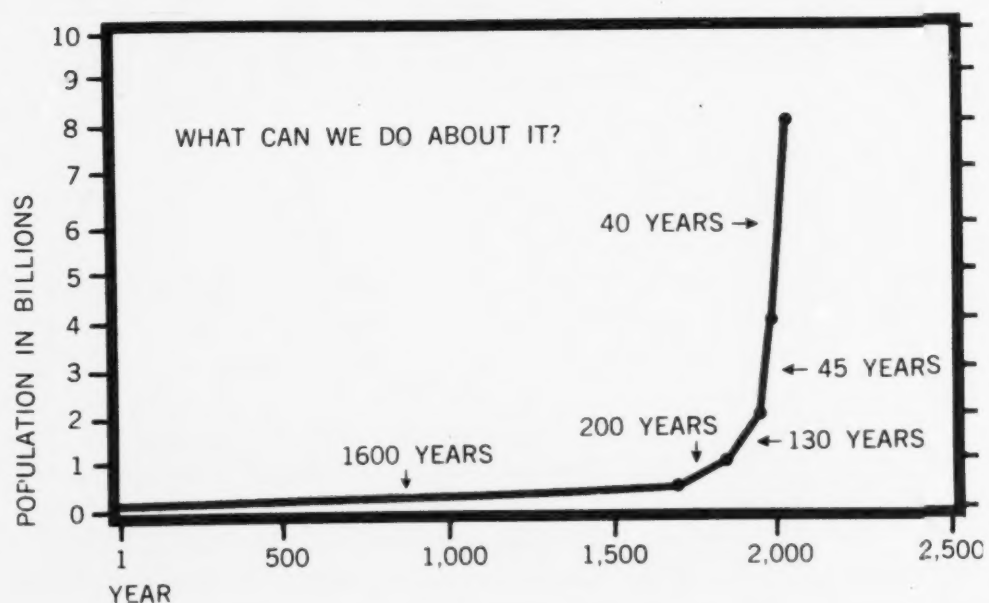
A study of the factors affecting the acceptability and effec-
tiveness of the IUD in humans is being conducted at the University of
California, under an NICHD contract. Information has been collected
on approximately 9,000 women provided with IUD's and follow-up ex-
aminations and surveys have provided data covering almost five years
of patient experience. When the study is complete, it should clarify
which women are the best candidates for the IUD on the basis of their
attitudes, and their social and physical characteristics.

Social, Psychological, and Economic Factors in Family Planning Acceptance and Population Change

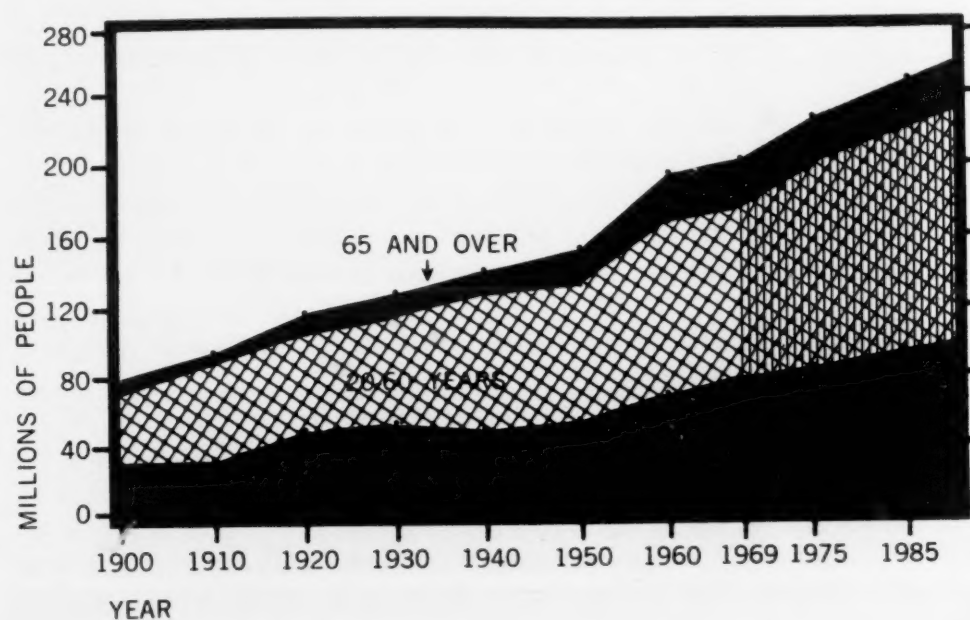
When the ideal contraceptives are developed, they still will
not diminish the world's population problems unless people are willing
to accept them, and to use them to plan families of limited size. The
need for knowledge concerning the conditions affecting that private de-
cision, and the public consequences of many similar reproductive de-
cisions and acts (namely, patterns of change in the birthrate and in the
total population size) is a matter of intense concern and programmatic
effort by the Institute.

Although the Institute's population research activities are re-
latively new, there are already significant signs of progress. The Prin-
ceton National Fertility Study, mentioned earlier, has proved to be a
rich source of information concerning family planning practices in the
United States. The investigators have found that, compared with
women interviewed in 1955 and 1960, the wives surveyed in 1965 still
wanted relatively large families of three or four children. As other in-
vestigators have noted:

THE WORLD POPULATION IS DOUBLING AT AN ACCELERATING RATE



TRENDS IN THE AGE DISTRIBUTION OF THE U.S. POPULATION



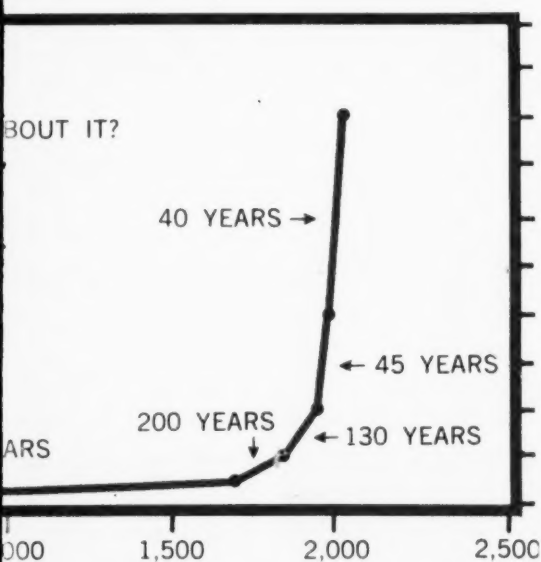
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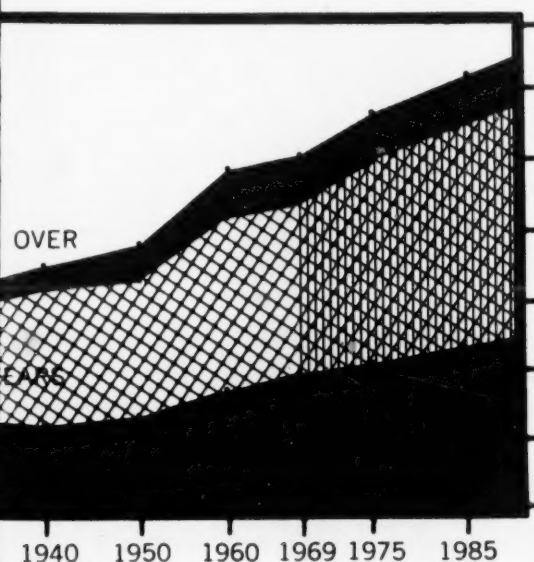
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DOUBLING AT AN ACCELERATING RATE



POPULATION OF THE U.S. POPULATION



"With little change in mortality, marriage patterns, or immigration, the three-child family would lead to a population of 312 million by 2000, and of 600 million by 2050. . . . Even the forecast for the year 2000 means a population so large as to imply a fundamental change in many aspects of our society. Americans may soon have to choose between the consequences of a very large population or a revision of their present values about marriage and childbearing."

The gap between intended and actual family size, even with the use of contraceptives, makes the intention seem even more ominous. As shown by the National Fertility Study, of the couples studied who intended to have no more children, less than one-quarter were completely successful in controlling their fertility. More than one-half of the women reported failure in timing one of their children, and a substantial proportion (one-third) of those who reported success in timing fertility were actually women who did not use contraception, but claimed to have wanted all of their pregnancies as soon as possible. Among mothers who still intended to have more children, 62 percent had already had one timing failure.

A significant proportion of American couples—perhaps 20 percent—have more children than they wish. This is due in part to the use of ineffective contraceptive methods, the failure to use methods regularly, and lack of access to methods such as the pill and IUD requiring medical supervision. The Princeton investigators predict that unintended births will probably decline as people's educational levels rise, contraceptive methods improve, religious resistance to many contraceptive methods decreases, and Government assistance to family planning programs increases.

A hopeful note concerning the effectiveness of family planning programs has been struck by a study of fertility and family planning in Taiwan. An investigator from the University of Michigan and his associates are cooperating with Taiwan agencies to analyze and assess the long-term effects of a family planning program within the context of social and demographic changes characteristic of a developing nation. The most important finding thus far is that those couples who enter the family planning program continue to maintain much lower than expected birth rates for many years, even if they stop using the method furnished by the program, or drop out of the program entirely. They have been motivated and enabled to find their own solution to the control of their fertility. Significantly, the evidence also indicates that the family planning programs has affected the birthrate over and above what might have happened as a result of social and economic changes. Information from this program is expected to be immensely valuable to all countries interested in fertility control and family planning.

Maturation and Aging

As any athlete or sports fan knows, the 20 or so years it takes to reach the peak of physiological development are followed only too soon by a gradual but steady decline of prowess, stamina, and coordination that makes 25-year-old superstars talk of "retirement," and gives 35-year-old ballplayers the epithet of "grand old men." The decline of intellectual skills occurs far more slowly, but is equally insidious and inexorable. The aging process, a natural continuation of the developmental cycle, begins long before one normally considers himself old, or even middle-aged, and proceeds to whittle away at one's abilities until physiological competence becomes so poor, and resistance to environmental stresses so weak that the individual can no longer survive. In humans, the process often takes far less than the allotted "three score and ten" years, and is almost always complete within 110 years.

As medical science progressively eradicates disease, aging probably will be the major health problem of the future. The Institute, with its commitment to research, provides extensive support for such research. The Institute's research is socially rewarding. The Institute's research studies by scientists aging as a cluster of problems and processes.

Unlike most fields of gerontology, the field of gerontology has as yet relatively little research in aging, and this field.

The Institute housed in the newly more, represents a process, and a unique programs within the years, having received since as early as 1990, simultaneously supporting programs of research in

While the Institute was founded gerontology as a science largely been described experimental knowledge has been provided

As medical science advances, and serious diseases are progressively eradicated, the developmental and aging processes will probably be the major determinants of a long, productive life. The Institute, with its commitment to the study of the total life continuum, provides extensive support for the study of aging in the hope that such research will lead to new ways to encourage healthier lives that are socially rewarding and contributory throughout the later years. The Institute's research program on aging encompasses animal and human studies by scientists in a wide variety of disciplines, and addresses aging as a cluster of interrelated biological, medical, and behavioral problems and processes.

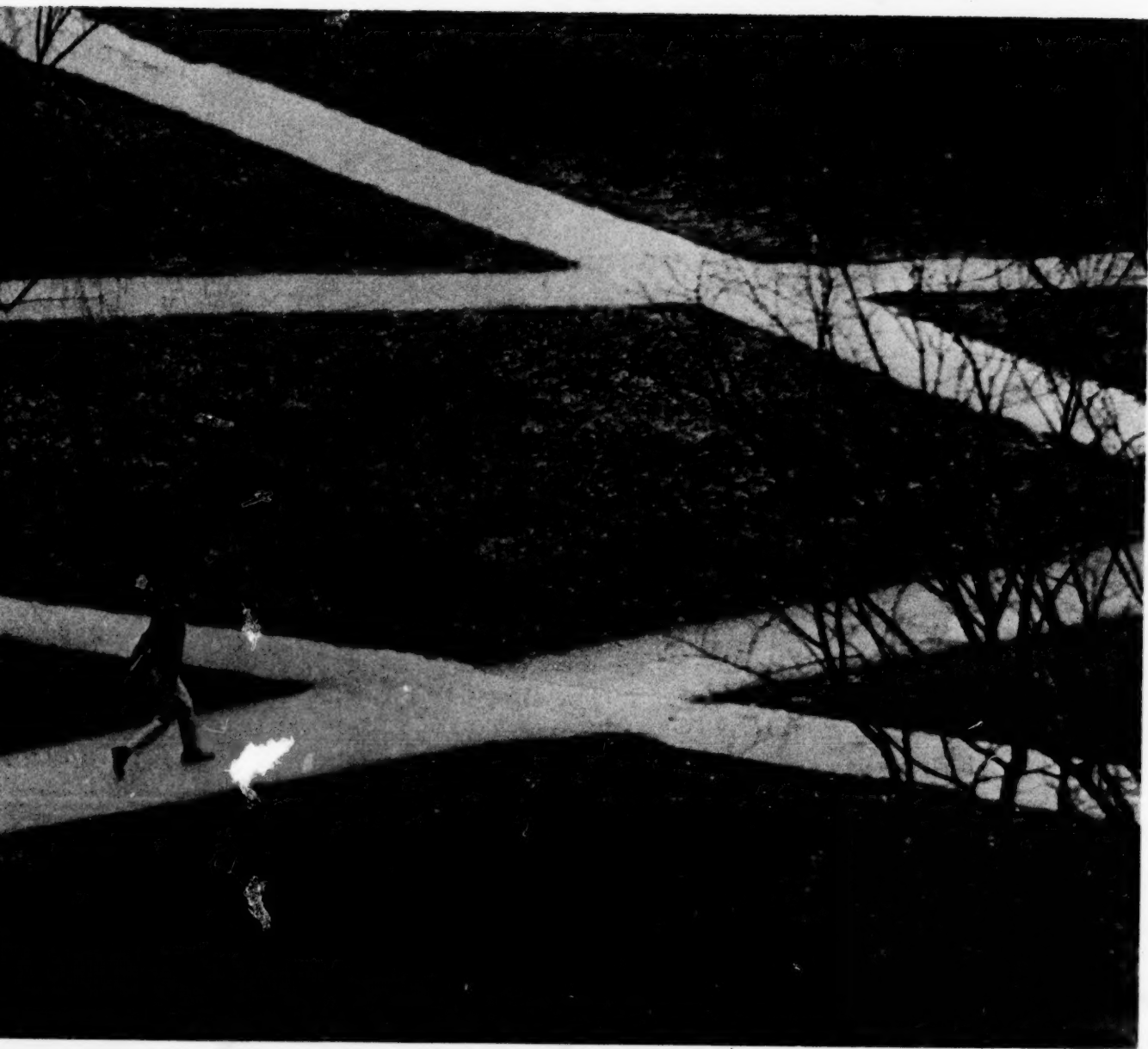
Unlike many other study areas supported by NICHD, the field of gerontological research is relatively new, and, despite its importance for the well-being of the Nation's growing elderly population, has as yet relatively few researchers. One of the major achievements of NICHD since its inception has been its encouragement of new research in aging, and its support for training to attract new scientists to this field.

The Institute's intramural program of research in aging, housed in the newly constructed Gerontology Research Center in Baltimore, represents a primary source of new insights into the aging process, and a unique resource for the Nation. Many of the research programs within the Research Center antedate the Institute by many years, having received continuous support from other NIH institutes since as early as 1945. Thus, NICHD now has the distinction of simultaneously supporting some of the country's oldest, and newest, programs of research in aging.

While progress in this field has been extensive since the Institute was founded in 1963, in keeping with the relative newness of gerontology as a scientific discipline, the majority of studies have largely been descriptive. As yet, only a limited body of theoretical and experimental knowledge is available. While invaluable documentation has been provided on the changes that take place physically and psy-

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chologically as organisms mature and grow old, there are only glimmers of insight as to why these events happen, or how. The biological mechanisms underlying the aging process have barely been explored, and basic questions concerning the nature of aging at the cellular and subcellular level are just beginning to be asked. Still, some provocative leads are already emerging.

The Basic Biology of Aging

The human body consists of approximately 60 trillion cells living together and conducting the activities necessary for its survival as an entity. Some of the body's cells, such as those in the brain, do not divide again once they have been formed early in life. Other cells divide repeatedly, replenishing themselves and replacing cells lost through injury. One of the major theoretical questions challenging the scientists studying aging is whether the biochemical processes that produce senescence are inherent in the body's cells, or whether the cells themselves are potentially immortal, but break down from certain interactions among themselves. (The possibility also exists that some of the body's cells are potentially immortal while others have life-spans that are intrinsically limited.) The answer to this question has profound implications for biology, medicine, and for man's own philosophical view of himself. It is being sought through vigorous support by the Institute's extramural research program for studies of aging in various cell types grown outside their normal sites in the body.

In one approach, cells are transplanted from a young donor through a series of young hosts, so that they can be kept alive far longer than they would have been in their original source. For example, the cells of transplanted rat skin can live twice as long as an entire rat, suggesting that while such cells are not immortal, they have greater potential longevity than is normally seen.

For many years, scientists thought that some cells could be immortal if removed from the body and grown in tissue culture—that is, in special nutrient fluids. They later found that such long-lived cells are genetically abnormal in ways resembling cancer cells. Most

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normal human cells divide a few times in tissue culture and then die. However, one type of normal cell, the connective tissue cell known as a fibroblast, has been found to divide about 50 times before it declines and dies. While such cell death might result from inadequate conditions in the culture medium, it seems more likely that the cells die naturally of internally caused senescence. If so, the fibroblast tissue culture may provide a system much simpler than the entire mammalian organism for the study of some aspects of aging. To encourage further research in this area, NICHD has sponsored conferences to consider the problems and opportunities of working with tissue cultures; has awarded a number of research grants to investigators working with transplant and tissue culture techniques; and has contracted with a university with particular competence in this field to provide appropriate cells to investigators, and to conduct training and workshops relevant to the study of such cells.

Another approach to the problem of aging focuses on the large, complex molecules such as DNA (deoxyribonucleic acid) that control the chemical activities of cells. These molecules of DNA are formed only at the time of cell division. Thus, in cells that do not divide, such as nerve cells, the DNA in their nuclei is as old as the organisms of which they are a part. It would not be surprising to scientists if, in the course of a man's lifetime, the thermal and chemical energies in these molecules' microenvironments bring about certain structural changes that mean less efficient functioning over time. The "error theory" of aging has therefore been proposed, which suggests that if alterations or errors occur in a DNA molecule, it will carry out its job of protein synthesis incorrectly, and will produce defective enzymes. To compensate for this error, more protein synthesis is needed. Since only defective protein can be produced, the vicious cycle continues until the cell, and eventually the organism, dies.

To test this theory, a scientist at the Institute's Gerontology Research Center has experimentally produced an artificial "error" in an animal's enzyme, and has confirmed that compensatory protein synthesis occurs. Proof is still lacking that this happens naturally.

One of the major biological questions in gerontological research concerns how parts of the genetic information of DNA remain unused during one portion of an organism's life and become functional during another. Inroads into this problem—which is fundamental to an understanding of cellular differentiation, development, and aging—have been made by several scientists at the Institute's Gerontology Center. For example, one study of age changes in the rat liver has shown that over time, alterations occur in the metal ionic environment of certain proteins (histones) in the cells. The changes, in turn, affect the way the histones interact with DNA and modify expression of the genetic code. Thus, a mechanism has been suggested for variable expression of DNA at different life stages.

Other studies at the Center have revealed that when pure DNA is stripped of its histone protein, it remains physically and functionally unaltered with age. Whether from the livers of young or old rats, chromatin DNA was found to show the same "melting" behavior (uncoiling and separation of its strands under heat)—a prerequisite for transcribing genetic information.

A related investigation by scientists at the Gerontology Center has been concerned with possible aging changes in the cells' machinery for protein synthesis. Their findings have indicated that when thyroid hormone is used to induce maximally a specific enzyme in rat liver cells, the cellular mechanisms in old rats are intact and competent to carry out the entire biochemical process of synthesizing protein.

Along a somewhat different line of inquiry, one scientist at the Gerontology Center has been exploring the provocative possibility that the total life-span, from fertilization through senescence to death, may be "programmed" genetically, and may follow a preset timetable. He has found, through manipulating the temperature or diet of the rotifer, a tiny aquatic organism, that its normal life-span of 18 to 20 days can be almost doubled. Even more importantly, he found that the two types of manipulations lengthen different parts of the life-span. Rotifers that had been fed at only half of their normal nutri-

tional level gained a longer life period, but did not live as long a period. By contrast, rats live a normally long period of egg-laying days with only a few days left for early life, and once in a while, by chance, the study suggests that longevity by manipulation may be able to choose to live longer.

An NIH study, too, dietary manipulation, calorically restricted, is a phenomenon is currently being studied.

Institute scientists have found that bioenergetic reactions such as functions such as the structures responsible for growth more fragile and with age. These findings do not react as well as demands of the cell.

Another study by Institute scientists suggests that collagen, body consists of glycosaminoglycans, certain alterations in the component of the changes in its amino acids, commonly associated with and pulmonary fibrosis of the aged. Collagen

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tional level gained additional days during the young, egg-producing period, but did not increase the length of their "postmenopausal" period. By contrast, rotifers exposed to reduced water temperatures had a normally long period of youth and fertility, but their older, post-egg-laying days were significantly increased. These results suggest that two different timetables may be programmed in the individual: one for early life, and one for later life. In addition to its theoretical importance, the study suggests that it may be possible one day to increase longevity by manipulating the environment or diet, and that one may be able to choose the period in which his years are extended.

An NICHD-supported scientist has confirmed that in rats, too, dietary manipulations can affect the life-span; if they are given a calorically restricted diet, their life-span can be increased. This phenomenon is currently under study.

Institute scientists have also been studying the control of bioenergetic reactions in tissues to understand why energy-dependent functions such as muscular work performance decrease during aging. They have found that within the cell, the membranes of mitochondria (the structures responsible for energy conservation and transduction) grow more fragile and susceptible to harmful environmental conditions with age. These findings may indicate that mitochondria from old rats do not react as well as those from young animals to the biochemical demands of the cell.

Another basic biological aspect of aging being investigated by Institute scientists concerns the age changes seen in connective tissues such as collagen and elastin. Much of the structure of the human body consists of giant molecules which are replaced slowly, and show certain alterations with age. One of these, collagen, the major protein component of the supportive tissues, is of great interest, since changes in its amount and character are apparent in diseases commonly associated with aging, including arteriosclerosis, osteoporosis, and pulmonary fibrosis, and are also seen in the wrinkled, sagging skin of the aged. Collagen consists of long linear molecules interconnected

by cross-links that give the protein stability and affect its physical and chemical properties. These cross-links are known to increase with age; their multiplication has been considered to be responsible for collagen's changed properties with aging. The nature of these links and the factors influencing their formation and breakdown have, until recently, been unclear. However, an NICHD-supported biochemist at Albert Einstein School of Medicine has now helped define the chemical basis of these changes. He has isolated four and identified two chemical groups in collagen that might be involved in the cross-linkage process. One of these, enosaline, can react chemically with the enosaline on a neighboring collagen molecule to form a paired compound that makes a firm structural link between the strands.

Investigations at the Gerontology Research Center have now provided evidence that, at the molecular level, the age-related changes in collagen fibers are caused by increased interaction among the elementary collagen fibrils. Drastic changes have been seen in the structural protein of maturing and of aging, but not of newborn rats. Apparently, cross-links are produced in the collagen fiber throughout the life-span of the animal. Cross-linking first occurs among subunits within the tropocollagen molecules laid down during fiber formation; cross-linking then spreads randomly until a matrix is built up which joins the tropocollagen units so that increasingly trapped collagen becomes progressively less soluble.

Studies by NICHD scientists on elastin and elastolytic enzymes in lung, blood vessels, heart, skin, blood, and pancreas have indicated that structural protein is normally maintained by a complex balance of elastolytic enzymes held in check by specific inhibitors. But disturbances of this balance occur in aging, and in specific diseases such as lung emphysema, severe atherosclerosis, and aneurysms of the vessel walls. Four elastolytic enzymes, which attack different kinds of elastin, have been characterized by these investigators, and an inhibitor against one enzyme has been identified in serum and found to change in strength with age. The effect of pituitary hormones on the activities of these enzymes has also been determined. All of these studies provide experimental evidence aimed at understanding why

elastic tissues become stiff and why medical procedures to

One theory of aging, suggesting that with increasing age, the body's cellular constituents gradually break down and are replaced by new ones, is being tested. Factors in aging, and how they relate to diseases common to old people, are being studied. NICHD-supported research has shown that a substance called antinuclear antibodies can cause clear reactions in 16 out of 16 patients with a prevalence of three per

The Physiology of Aging

Basic questions about aging are being asked at the physiological level. Answers are equally provocative. For example, as people age, there is a deterioration of many body functions, yet the rate of change varies from individual to individual. Is there a set pattern of change for all systems of the body, or do some systems change more than others? Do the changes occur in a steady, continuous fashion, or are there plateau periods? Do the changes continue until certain functions are lost, or do they change until certain functions are lost? Are there some diseases that are accelerated or retarded rates of aging? Do different aging patterns exist? Answers to these and other questions are being sought by scientists in a comprehensive, coordinated program of research on the normal, healthy individual.

Previous studies have been conducted in order to

in stability and affect its physical and chemical links are known to increase with age; they are considered to be responsible for collagen aging. The nature of these links and the formation and breakdown have, until recently, been unknown. A NICHD-supported biochemist at Albert Einstein College of Medicine helped define the chemical basis of collagen cross-linking. He has identified four and identified two chemical groups involved in the cross-linkage process. These groups react chemically with the enosamine on a collagen molecule to form a paired compound that makes the collagen strands more rigid.

Scientists at the Gerontology Research Center have now shown that, at the molecular level, the age-related changes in collagen are caused by increased interaction among collagen molecules. Drastic changes have been seen in the collagen of old and of aging, but not of newborn rats. The changes produced in the collagen fiber throughout life are due to cross-linking first occurs among subunits of collagen molecules laid down during fiber formation; then, later, randomly until a matrix is built up which traps collagen molecules that increasingly trapped collagen become rigid.

Scientists on elastin and elastolytic enzymes in heart, skin, blood, and pancreas have shown that elastin is normally maintained by a complex system held in check by specific inhibitors. But changes occur in aging, and in specific diseases such as atherosclerosis, and aneurysms of the aorta. Enzymes, which attack different kinds of elastin, have been identified by these investigators, and an inhibitor has been identified in serum and found to be related to the effect of pituitary hormones on the degradation of elastin. The effect has also been determined. All of these studies have provided evidence aimed at understanding why

elastic tissues become less resilient during aging, and in discovering medical procedures to ameliorate these changes.

One theory of the mechanism of aging suggests that with increasing age, the body increasingly produces antibodies against its own cellular constituents. It is known that autoantibodies in the plasma increase with age. Further, autoimmunity has been implicated as a factor in aging, and has been shown to be associated with a number of diseases common to old age, such as arthritis, diabetes, and cancer. An NICHD-supported researcher studying autoimmunity has found evidence that gives substance to the theory. By studying the prevalence of antinuclear antibodies in people of various ages, he has found antinuclear reactions in 16 percent of people over 60, compared with the prevalence of three percent seen in people under 60.

The Physiology of Aging

Basic questions concerning the nature of aging are being asked at the physiological as well as the biochemical level; the answers are equally provocative and elusive. It is well known that as people age, there is a deterioration of almost all their capacities and bodily functions, yet the timetable of aging seems to differ from individual to individual. Is there a basic underlying aging process? Do the various systems of the body age concurrently, or are some more long-lived than others? Do the changes seen with aging progress gradually or are there plateau periods in which the body's functions are essentially unchanged until certain major physiological or psychological crises occur? Are there some individuals in whom all systems age at an accelerated or retarded rate? Do men and women age differently? Are there different aging patterns among members of various generations? The answers to these and other questions are being sought by NICHD scientists in a comprehensive study, begun 10 years ago, of aging in normal, healthy individuals.

Previous clinical studies on the aging process had usually been conducted in chronic disease hospitals or in old-age homes,

where the aged populations—often ill, and from poor, disadvantaged backgrounds—represented a skewed and sickly sample of the elderly. By contrast, the more than 600 men chosen for this study are highly *educated, happily married, successful individuals who are employed or retired from professional or administrative occupations*. They range in age from 18 to 103. Every 18 months (or every year for those over 70) they spend two and one-half days undergoing a battery of biological, biochemical, psychological, and physiological tests. The order of tests conducted at the NICHD Gerontology Research Center is rotated so that the test cycle is complete every four or six years.

A longitudinal study such as this attempts to show how given individuals change over their adult life-span. It obviously requires many generations of researchers to document the entire life cycle of many individuals. The 10-year sample obtained to date represents only about one-seventh of the information to be gained. Nonetheless, important findings have already emerged concerning general aging patterns. The study has been designed to test many aspects of physiological function when people exercise or do work. As expected, comparison of subjects of various ages shows that muscle strength and endurance both decline with age. In addition, the heart and lungs are progressively less efficient during exercise; with advancing age, the heart pumps less blood, the lungs absorb less air, and both take progressively longer to return to normal once the exercise stops. Functions requiring coordination (such as cranking a handle, or breathing to maximum capacity), decline more drastically than the physiological functions on which they are based, such as muscle strength or vital capacity.

The Relation of Aging to Disease

A central problem for medical practitioners and researchers alike is to separate the signs of disease from the physiological changes normally characteristic of healthy individuals at various stages of life. This problem is particularly important for physicians such as general

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practitioners and internists whose patients consist largely of aging and aged individuals. Most standards of normality in medical practice are based on tests with healthy young adults, such as medical students; they may represent what a typical of 20-year-olds, but not what is normal for older people. Thus, for a healthy old man, a test of blood pressure, lung capacity, basal metabolic rate, and blood sugar level might suggest that he has high blood pressure, emphysema, hypothyroidism, and diabetes if the same standards were used for him as for a young man. Indeed, using standard diagnostic levels of glucose tolerance, almost 50 percent of those over 60 would be labeled as diabetic.

As an aid in studying age differences in sickness and health, scientists at the NICHD Gerontology Research Center have developed a new technique that enables them to study how the bodies of young and old respond to sugar and to insulin, in order to distinguish between healthy and diabetic responses. NICHD scientists have devised an externally applied system that overrides the body's own control mechanisms, and permits the experimenter to regulate blood sugar levels. The investigators have been able to show that young adults require about twice as much sugar as older subjects to produce comparable blood sugar levels. Further, older subjects maintain high blood sugar levels more readily than the young, requiring a smaller boost in the rate and amount of sugar to do so. These results suggest that the ability to metabolize glucose decreases with age. Such studies should aid in distinguishing the normal concomitants of aging from metabolic disturbances requiring medical intervention.

Behavioral and Social Aspects of Aging

Since the work of Pavlov, psychologists and physiologists have devoted considerable attention to the comparative study of learning in man and animals. They have explored the effects of many variables on the abilities of animals and humans to acquire new patterns of behavior, to solve problems, and to remember what they have learned. Yet the effects of aging on learning ability have been given relatively

little study. As with the learning behavior are animals, or young coll

The Institute studies which attempt fuller understanding and ages. As the population increasingly important to businesses, and the reason. Through such understanding in the elders the experience agility most often seen

Although in learning than younger individuals that may be used in later years. Investigators have found that the verbal associations (enhanced if they say learned is presented investigator of this study young and old alike, converted into its auditory. Old people, he said. Thus, their learning auditory stimulation.

Scientists many of the intellectual are not as severe as 60) do not learn to subjects (under 50) who sure (within four seconds which to respond (electrically, and they respond

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psychologists and physiologists to the comparative study of learn- explored the effects of many varia- umans to acquire new patterns of remember what they have learned. ability have been given relatively

little study. As with the "norms" of medicine, the notions of normal learning behavior are based largely on research using relatively young animals, or young college students as subjects.

The Institute has sponsored and stimulated a number of studies which attempt to fill this gap in research knowledge, to give a fuller understanding of the mental capacities of man as he matures and ages. As the population of elderly persons grows, it becomes increasingly important to recognize their intellectual strengths and weaknesses, and the reasons for age-related changes in thought processes. Through such understanding, it might be possible one day to combine in the elders the experiential wisdom of many years with the mental agility most often seen in the young.

Although in general, the elderly have more difficulty in learning than younger individuals, new findings and techniques are emerging that may be used to improve their learning abilities and enrich their later years. Investigators at the NICHD Gerontology Research Center have found that the ability of aging individuals to learn and retain new verbal associations (as in learning a new foreign vocabulary) can be enhanced if they say their responses aloud, or if the material to be learned is presented aloud, as well as shown visually. The principal investigator of this study believes that during the learning process, for young and old alike, verbal material presented visually is normally converted into its auditory or spoken equivalent before it is stored in memory. Old people, he suggests, have difficulty in making this conversion. Thus, their learning and memory storage benefits from providing direct auditory stimulation.

Scientists at Duke University have been discovering that many of the intellectual, and even neurological, deficits of the elderly are not as severe as had been thought. For example, older people (over 60) do not learn to make verbal associations as well as younger subjects (under 50) when their responses must be given under time pressure (within four seconds). But if they are given a longer period in which to respond (eight seconds), their performance improves dramatically, and they respond, like the younger subjects, within less than the





allotted time. The investigators have found that the main difference between the two age groups is in their response to the stress of learning and being tested. Physiological measurements before, during, and after the learning experiment showed that for both young and old subjects, blood levels of free fatty acids (an index of anxiety) rose during the learning task. But in old subjects, the levels started out higher, remained higher throughout the task, and took longer to return to their original base line. It appears that anxiety makes learning more difficult for the elderly, particularly when they are faced with relatively complex tasks. The Duke scientists believe that to cope with this anxiety, older persons might subconsciously disengage themselves from the learning task, essentially choosing to perform at less than full intellectual capacity rather than undergo the strain of trying their very best under pressure.

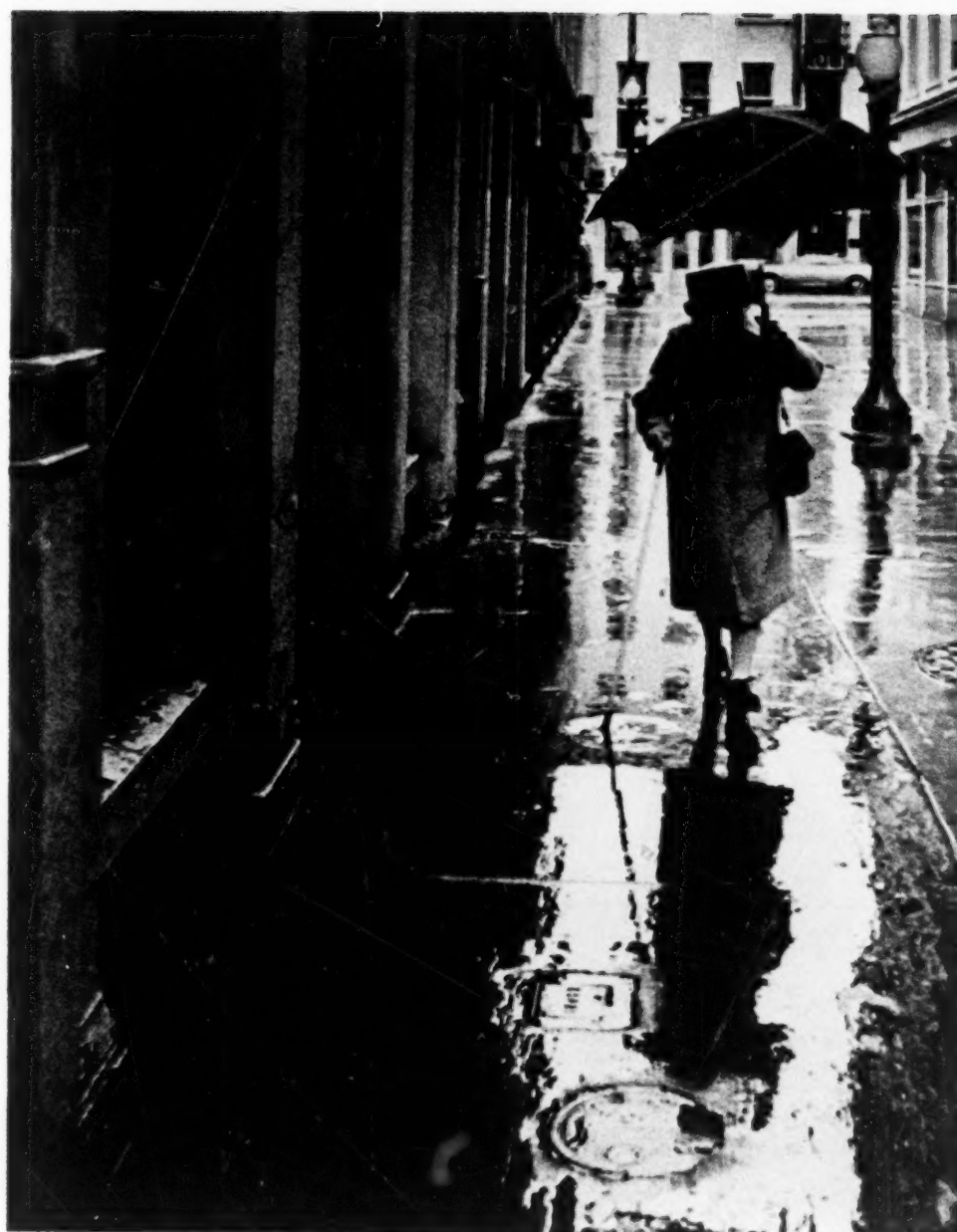
These same scientists have also been studying how aging affects the speed with which people respond to environmental events. Measuring simple reaction times to sound or to light, they found that while older subjects (between 68 and 86) were significantly slower than young athletes (between 18 and 27), their reaction times were not significantly slower than those of young nonathletes. Thus, individual differences in exercise and physical fitness seem to affect reaction time more than age differences. These data challenge the notion, based on previous reaction-time experiments, that decreased central nervous system function accounts for the slowing of reactions in the aged, and suggests instead, that exercise, or lack of it, may be at least as important. Perhaps with a proper program of exercise, the alertness and responsiveness of the elderly could be significantly improved, as well as their learning ability.

In addition to suggesting methods for improving the intellectual competence of the elderly, psychological studies by Institute scientists have suggested significant new ways to enhance their health as well. Two researchers at the Gerontology Research Center have shown that patients with abnormal heart rhythms (arrhythmias) can learn to control their cardiac rhythms at will if they are given a special type of

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training. The patients are told the nature of normal cardiac rhythm, and how their rhythms differ from normal. During training, each patient is given beat-to-beat feedback about his heart rate, so he can test how various kinds of behavior affect it. Within each training session, his performance is compared with that of previous sessions. The subject learns the results of electrophysiological and laboratory tests, as well. Clinical improvement is judged by several criteria: how the patient feels (including exercise tolerance, dizziness, "skipped beats," and the like), electrocardiograms taken at rest and during exercise, and diagnostic physical tests of cardiac function. To date, of the six patients to whom training has been given, three have shown a striking ability to affect their heart rate. One can turn his irregular beats either on or off at will, and one can turn them off. By learning to exercise such control, patients with disturbed cardiac function might lead more normal lives and avoid more severe and often fatal disturbances of heart rhythm.

The social and psychological aspects of aging have been given increasing attention by Institute-supported scientists, although this area is still under development. To help attract professionals to this field, grants have been given to several institutions to train researchers in adult development and aging. At the University of Chicago, a number of trainees in this program are specializing in the social and psychological problems of middle and old age. They are trying to find answers to such questions as: What are the life patterns of successful, middle-aged persons? What events lead middle-aged men to perceive themselves as burning out in their career and family roles?

To understand better how early life characteristics relate to adult behavior and patterns of aging, one Institute grantee is studying the subjects of three longitudinal studies, and their spouses, children, and parents. For given individuals, early behavior and growth characteristics are related quantitatively to those of late childhood and adulthood. Similarities between children and their parents are noted, as well, and the children's personalities and physical and intellectual

measurements
ages.

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normal cardiac rhythm, during training, each patient's heart rate, so he can stay within each training session's previous sessions. The physical and laboratory tests, physical criteria: how the patient's heart rate, "skipped beats," and during exercise, and during exercise, and during exercise. To date, of the six patients, five have shown a striking increase in irregular beats either before or after learning to exercise. This might lead more to a fatal disturbances of

Aspects of aging have been studied by scientists, although they do not attract professionals to study aging in institutions to train researchers. At the University of California, San Francisco, researchers are specializing in the study of aging and old age. They are studying what are the life patterns of aging. Patients lead middle-aged lives, and their career and family

Aspects of aging relate to the study of aging. The Institute grantee is studying the life patterns of aging, their spouses, children, and growth characteristics of aging. The ultimate stages of human maturation, and new methods are discovered for enhancing the quality of years, as well as their quantity, the Institute's primary goal of encouraging optimal human development throughout the life cycle will come closer to fulfillment.

measurements are compared with those of their parents at the same ages.

Among the NICHD-supported studies of the effects of the social environment on the aged, one investigator has compared the psychosocial characteristics of residents of homes for the aged with those of individuals waiting to enter such homes, and those living in the community. He has shown that institutionalized individuals are less oriented toward everyday reality, are more preoccupied with the functioning of their bodies, have less involvement in relationships with others, and have more impaired memory than those living outside old-age homes.

Other studies have explored the responses of individuals to a major milestone of the older years—retirement. Investigators at Duke University, comparing how white- and blue-collar workers adjust to retirement, have found that while the blue-collar worker is initially relieved to stop working, he brings less personal and social resources to retirement than the white-collar worker, and in the long run, without work to regulate and stabilize his life, often becomes very dissatisfied.

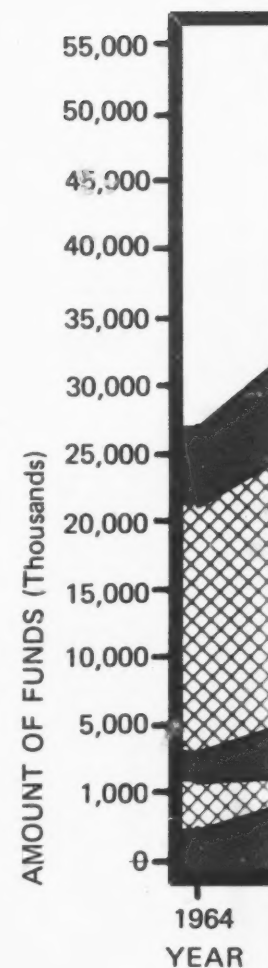
Studies such as these, as well as training programs and conferences supported by the Institute, are helping to pave the way for a behavioral science of the adult years. While scientific knowledge is still virtually nonexistent concerning the social and psychological meaning of adulthood and aging for the individual and for his society, Institute programs are encouraging initial explorations of this essential aspect of the life cycle. Through NICHD biological and behavioral science programs in aging, the notion of adult development as a dynamic, emergent process in its own right, rather than as the end product of childhood and adolescence, is gaining wider acceptance. As greater understanding emerges concerning the ultimate stages of human maturation, and new methods are discovered for enhancing the quality of years, as well as their quantity, the Institute's primary goal of encouraging optimal human development throughout the life cycle will come closer to fulfillment.

**APPENDIX:
Trends in Funding and
Program Development**

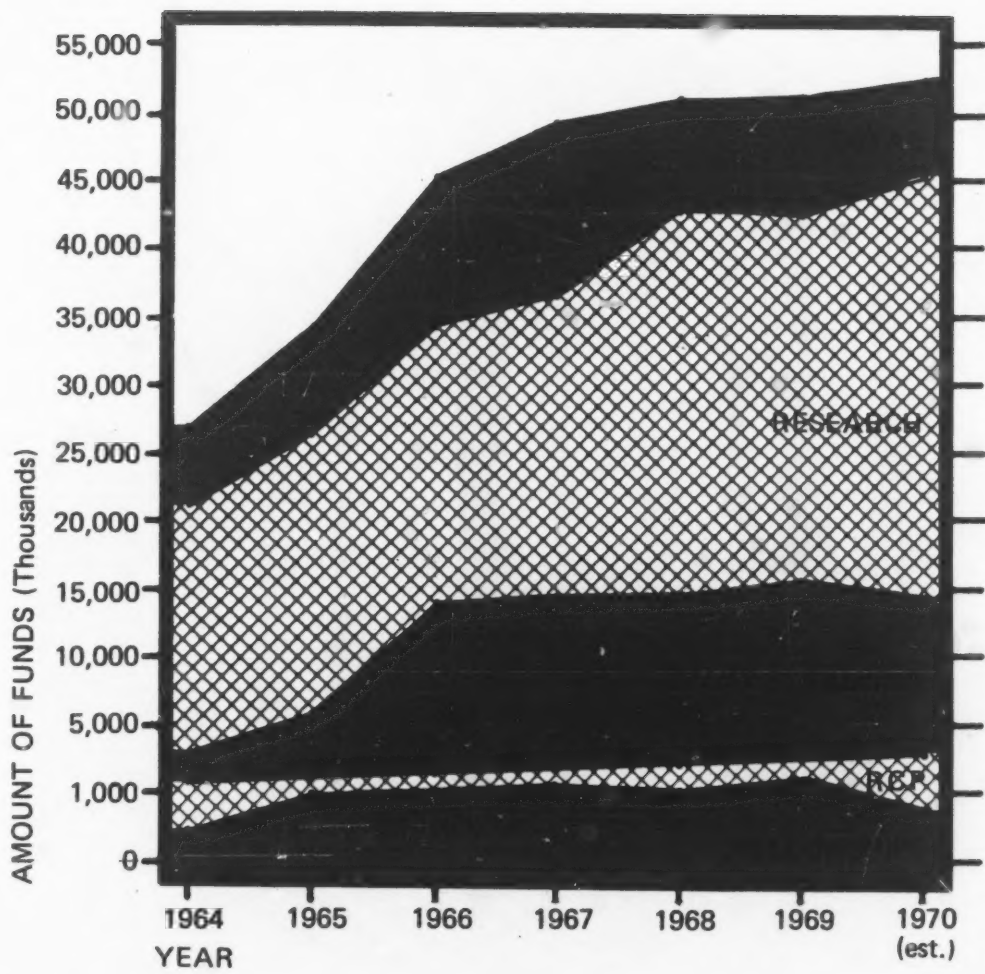


NICHD GRANTS, FISCAL YEAR 1964 - 1970

TYPE OF GRANT	AMOUNT OF FUNDS (Thousands)		
	1964	1969	1970 (est.)
Research	21,612	37,596	40,080
Training	3,515	10,012	9,392
Research Career Programs	1,241	2,452	2,744
Fellowships	649	1,740	872
TOTAL	\$27,017	\$51,800	\$53,088



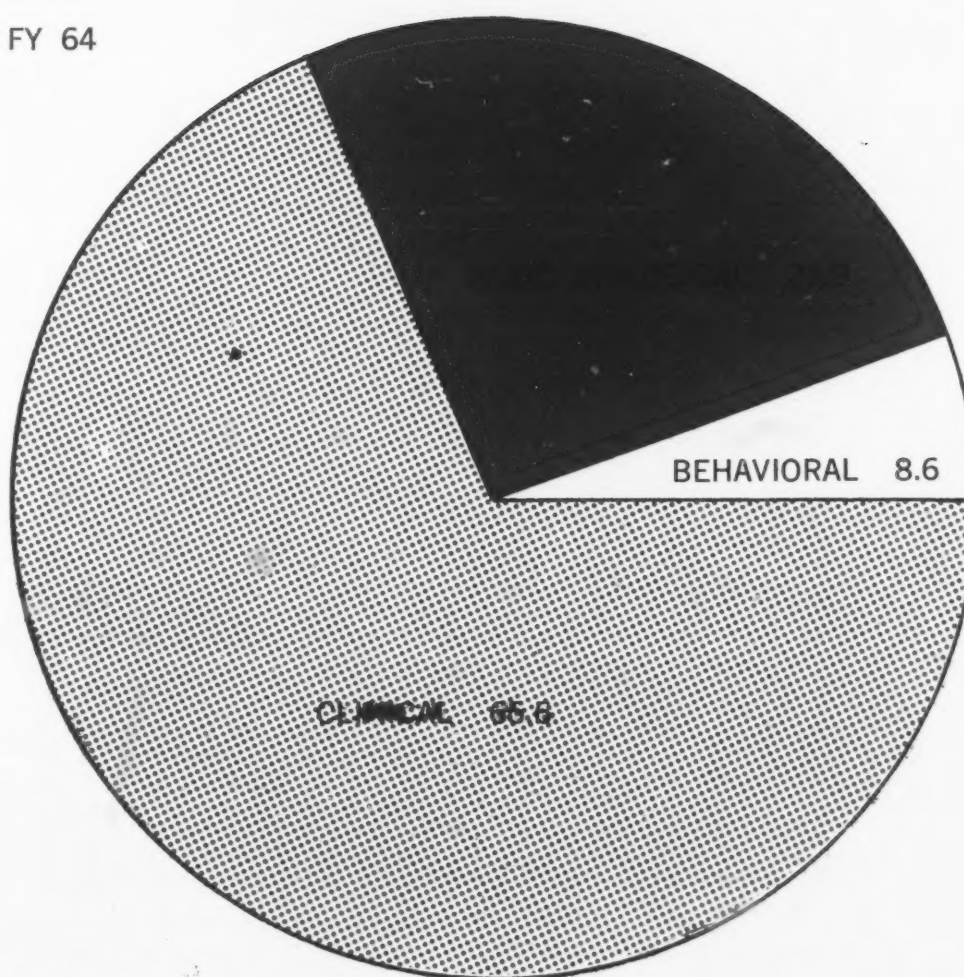
thousands)	1970 (est.)
	40,080
	9,392
	2,744
	872
	\$53,088



TOTAL TRAINING FUNDS (%)

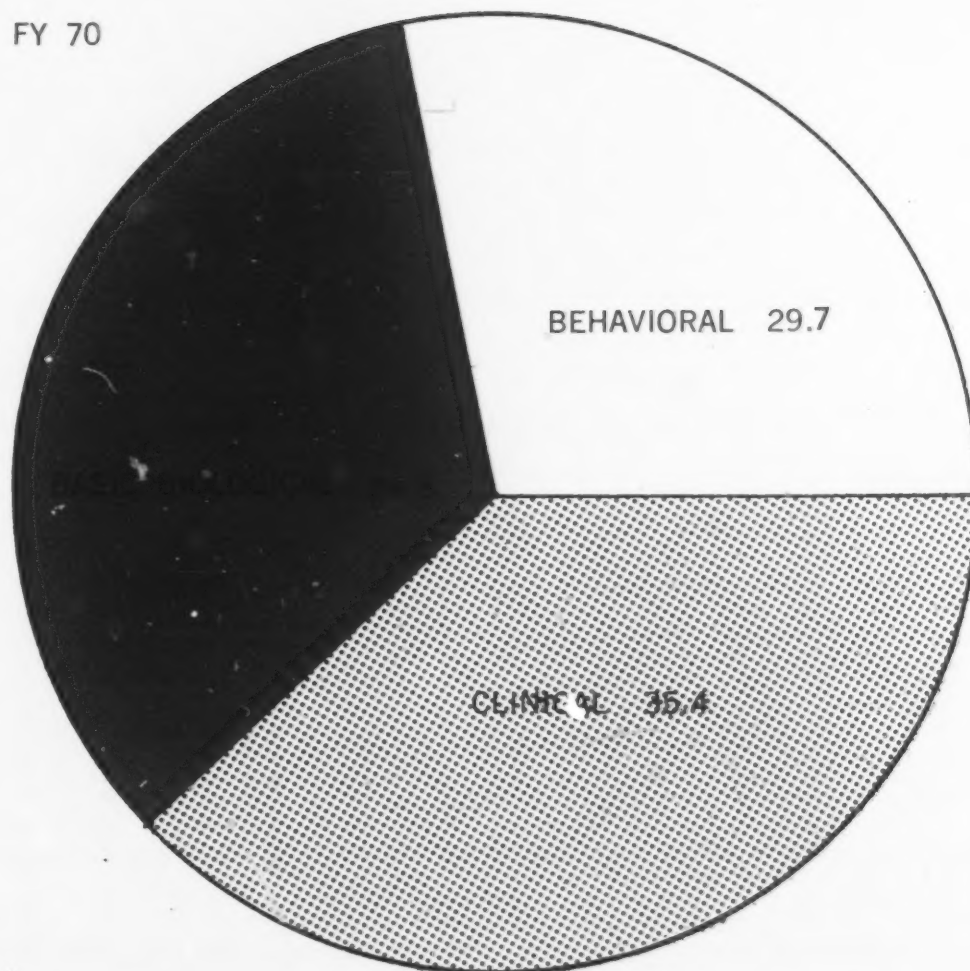
FY 64

FY 70



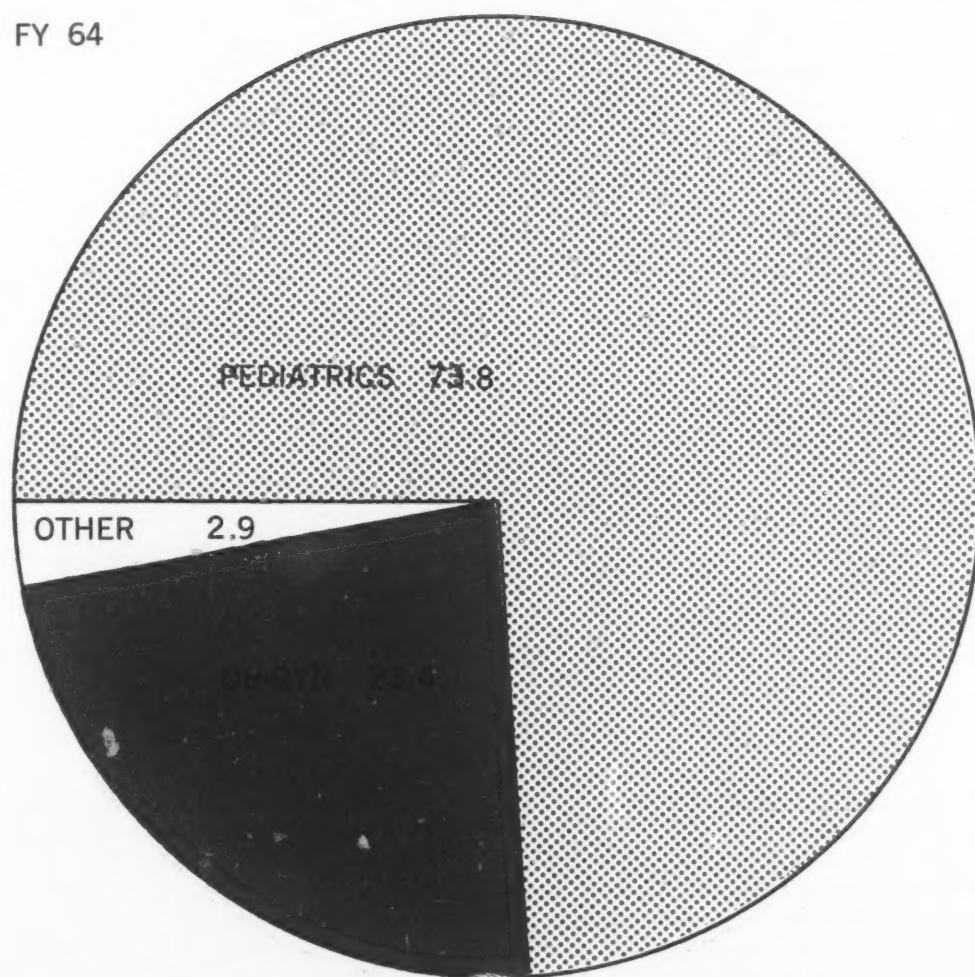


FY 70



TRAINING GRANTS IN CLINICAL DEPARTMENTS % (\$)

FY 64



NTS % (\$)

FY 70

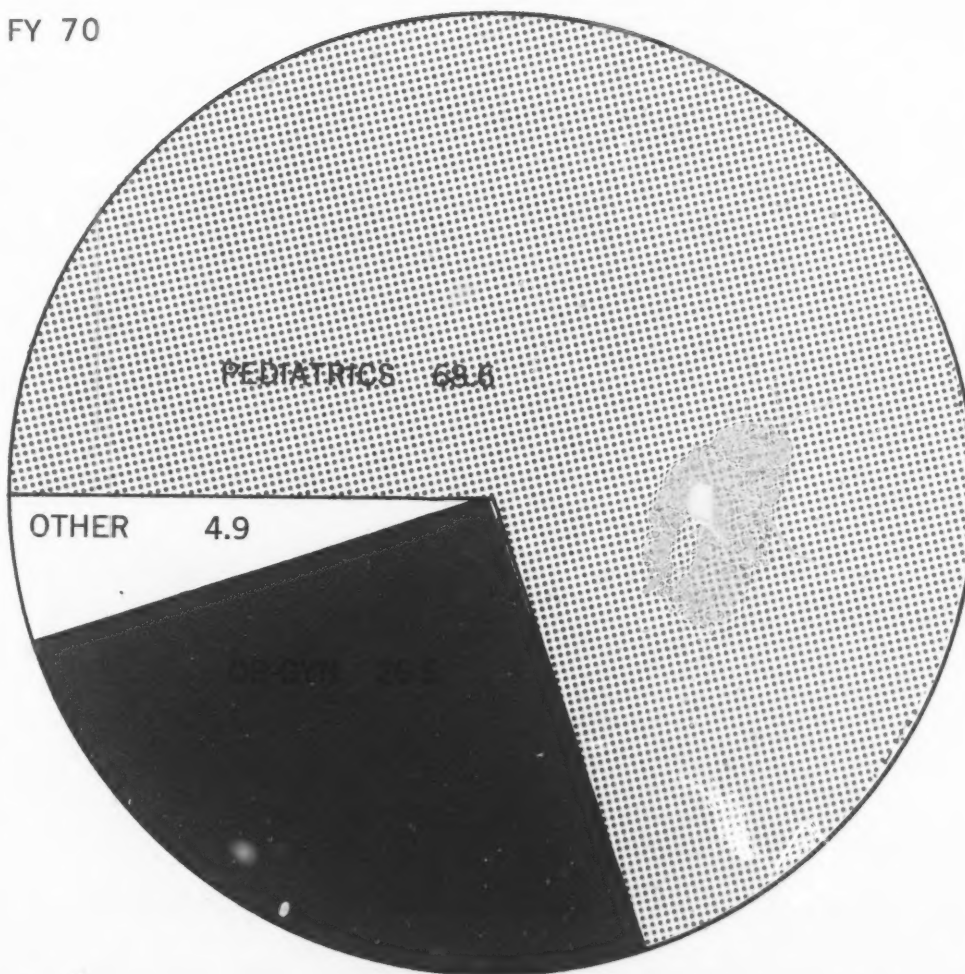


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